Docket No.: 01527/100L635-US1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Arthur Ashman

Application No.: 10/789,442 Confirmation No.: 5006

Filed: February 26, 2004 Art Unit: 1711

For: CROSSLINKABLE POLYMERIC MATERIALS AND THEIR APPLICATIONS Examiner: S. W. Berman

Declaration of Dr. Robert S. Langer under 37 C.F.R. § 1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, ROBERT S. LANGER, do hereby declare and state the following:

1. I, Robert S. Langer, am a citizen of the United States, and I am more than twenty-one years of age.

2. I make this declaration in support of the above-identified application, U.S. Serial No. 10/789,442 ("the '442 application").

3. I am not a named inventor of the '442 application. Furthermore, I have not been paid for my opinions expressed in this declaration, but I have been compensated for my time in reviewing the studies mentioned in this Declaration and in preparing the Declaration itself.

4. I presently hold the position of Institute Professor at the Massachusetts Institute of Technology (MIT). I have been elected to the Institute of Medicine of the National Academy of Sciences, the National Academy of Engineering, the National Academy of Sciences and the National Inventors Hall of Fame.

5. My qualifications as a scientist, and in particular in the field of polymer chemistry, are set forth on the copy of my curriculum vitae, which is attached as **Exhibit A**.

6. I have read and am familiar with the specification of the '442 application as filed, the Office Action mailed March 7, 2007, U.S. Patent 6,933,328 to Schacht (the Schacht Patent) as well as U.S. Patents 5,837,752 (the '752 patent) and 5,902,599 (the '599 patent) on which I am an inventor.

7. Since December, 2004, I have acted as a paid Consultant for Bioplant R&D, LLC, a company owned by Dr. Arthur Ashman, an inventor on the '442 application and owner of the licensee, A. Enterprises. Since July 2006, this position has been unpaid.

8. It is my understanding that the Examiner believes that the claims in '442 application are obvious over the Schacht patent since Schacht discloses a cross-linkable prepolymer, a polymer, and a mineral biologically active component for bone implant, and it would be obvious to modify the Schacht process to form the claimed bone substitute and polymer compositions as claimed in the '442 application. Similarly, it is my understanding that the Examiner believes claims in the '442 application to be obvious over Schacht in view of the '752 patent or the '599 patent since these patent teach methacrylic acid dianhydride polymers. Further, it is my understanding that the Examiner believes the claims in the '442 application to be obvious over the '599 patent in view of Schacht since the '599 patent teaches that the biodegradable polymer networks of the Schacht patent can be combined with other materials.

9. At the request of Bioplant R & D, I have reviewed various studies that have been conducted using cross-linkable polymers in combination with bone substitute materials in dental applications. As a result of this review, as discussed below, I have come to the opinion that it is very difficult, if not impossible, to predict how such combinations will perform in dental applications. As a result, the Examiner's statements of obviousness are not supported by the science, and the claims of the present invention are not obvious in view of the cited prior art patents.

10. A summary of the studies I have reviewed, and on which my opinion is based, are set forth below:

The Huys Study (University of Ghent)

11. I have reviewed the results of a study of the use in dental applications of materials covered by the Schacht patent, which study was performed by by Dr. Luc Huys at Ghent University in collaboration with Dr. Arthur Ashman.

12. This study provides data on the use of particular bone substitute materials in the mandible of sheep with and without concomitant placement of dental implants into the jaw bone of sheep.

13. According to the Research Proposal provided by Dr. Ashman (Exhibit B), the polymer material used in this study was a light cured polymer ((polylactide) P-LA 0.5 and (1,6-hexanediol) HXD 20/1 + BM + 2/3 molar fraction Hema. 5 mole%

camphoquinine and N-phenylglycine were also added. According to Dr. Ashman, the samples were developed and provided by Dr. Schacht, a colleague of Dr. Huys at the University of Ghent.

14. According to Dr. Ashman, the bone substitute material was Bioplant® HTR® as provided by Dr. Ashman. The HTR was mixed in a 50/50 ratio with the light curable polymer. It should be noted that in the Schacht patent there is no disclosure of mixing bone substitute material with a polymer. Rather, in the Schacht patent the bone substitute material (HTR) is packed around an implant and covered with a layer of light curable polymer.

15. Seven sheep and a total of 22 implants were studied. The parameters of the study are described in **Exhibit B** and the implant locations are given in the table in **Exhibit C**.

16. My understanding of the study is as follows:

a. Some of natural teeth of the animals were removed. In some cases the HTR/polymer materials was used to fill the socket and tissue was sutured over the site. In other cases the sockets were allowed to heal, and then the gum tissue was excised and reflected. Holes were drilled into the underlying jaw bone and implants were installed in the holes. The area of the sockets around the implant was packed with the HTR/polymer mixture and the tissue was sutured about the post part of the implant which extended above the gum line.

b. The insertion of bone replacing materials was determined by X-ray. The animals were then examined periodically ovar a period of 6 months. In the premolar region, the changes in the bone density revealed the site of bone regeneration on both sides. If this area showed a homogenous radiolucency, one biopsy sample was taken. If the density of healing bone was markedly different, two samples were examined (medial and distal analysis of biopsy samples). Trephine burrs were used to take biopsy samples in the healing bone. For metallic implants, the screw was removed, and the bed was removed by block resection. A total of 20 tissue samples were taken.

c. For the histologies, formalin-fixed undecalcified samples were dehydrated and embedded in methylmethacrylate at 4°C. Five μm thick sections were cut with a diamond knife, and the setions were stained with haematoxylin and eosin, toluidine blue, according to Goldner's trichrome method for light microscopy.

17. For sheep #0767, a marked connective tissue proliferation and inflammatory reaction was a characteristic finding. Granulonmatous proliferation, and foreign body giant cells were seen extensively with no bone formation in the right mesial and some new woven type bone formation in the right distal. (See Exhibit D).

18. For sheep #4562, dense chronic inflammation reaction appeared in the soft tissue without any sign of new bone formation (see Exhibit E, slides 1 – 2).

19. For Sheep #5261, a titanium (Ankylos®) implant was used. There is tissue at the apical 1/3 of the implant (See Exhibit F, slides 1-2) and substantial inflammation. Slides 3 – 4 (Exhibit F) show the failure of the implant and squamous cell epithelium lining, appearing like a periodontal pocket.

20. For Sheep #0577, the screw titanium implant was embedded into connective tissue, which cannot provide a stable anchorage for it. An intensive chronic inflammatory reaction was seen (Exhibit G, slide 1) as well as inflammation and connective tissue bed around the implant, (Exhibit G, slide 2). This specimen has some bone formation; however, a thin connective tissue layer around the implant hampers the stable fixation of the implant (Exhibit G, slides 1, 3, and 4).

21. In summary, at the termination of the 6-month study, 5 (22.7 %) implants remained. Each of these remaining implants showed unsatisfactory clinical osseointegation. The only acceptable bone formation with these implants was on the apical part of the implant.

22. Based on the results of this study, it is my opinion that a curable composition of the polymers disclosed in the Schacht patent mixed with the bone substitute Bioplant® HTR® is unacceptable as a bone implant material.

The Brooks (LSU)

23. I have reviewed the results of a study done by Dr. MaryAnn Brooks and Dr. Raymond Yukna at Louisiana State University (LSU) in collaboration with Dr. Kristi Anseth (a co-inventor on the '599 patent) and Dr. Arthur Ashman. This study was an evaluation of the dental material's handling and effectiveness in calvarium and mandibular defects in the rabbit.

24. According to Dr. Ashman, the study used the anhydride polymers as described in the '442 application. The polymers were hardened using light, but no chemical hardening was provided. The study was stopped prematurely due to rabbit death. The study proposal is provided in Exhibit H and the results were written in a thesis by Dr. Brooks (Exhibit I)

25. The bone substitute was Bioplant® HTR® provided by Dr. Ashman. Bioplant® HTR® was combined with the anhydrides to give the four polymer materials used in this study (LC1, LC2, LC3, and LC4). Dr. Ashman informed me that these materials were:

LC1 – anhydrides material alone (MCPP (methacrylated carboxyphenoxy-propane) and MSA (methacrylated sebacic acid) in an IPN (semi-interpenetrating network))
LC2 – anhydrides with calcium carbonate
LC3 – anhydrides with Bioplant HTR®
LC4 – anhydrides with calcium carbonate and Bioplant HTR®

26. Forty-eight rabbits in six groups were tested using LC1, LC2, LC3, LC4, Bioplant® HTR® only, and a negative control.

27. As described in the study proposal (Exhibit H), an 8 mm trephine bur was used to create two side-by-side circular defects lateral to the midline suture in the parietal bone. Each Calvarium defect was grafted with one of the test compounds or left alone as an ungrafted control. The compounds were cured for five minutes. The rabbits were killed at the end of 4 or 8 weeks after grafting, and histological analysis was done of block tissue samples. In vitro assays of the compounds were also provided using rat osteosarcoma cells.

28. According to Dr. Brook's thesis, a significant number of animals exhibited morbidity, causing an early termination of the study. Histological evaluation of positive control sites (HTR®) showed few inflammatory cells, connective tissue and sparse new bone formation (Exhibit I, slides 5 – 6). The negative control showed no inflammatory cells, connective tissue, and new bone (Exhibit I, slides 7 – 8). The test sites for LC1 – LC4 each showed inflammatory cells, necrotic bone with very few new bone particles, plasma cells, and giant cell reactions around the LC test material.

29. According to Dr. Ashman, biopsy results showed methylacrylic acid was given off and not neutralized. This is understood to have caused tissue necrosis and, in some instances, death.

30. Based on the results of the Brooks study, it is my opinion that a curable composition of the anhydride polymers requiring 5 minutes cure time is not an optimal bone implant material for dental purposes.

The Yukna Pilot Study (LSU)

31. I have reviewed the available results of a study done by Dr. Raymond Yukna at LSU in collaboration with Dr. Arthur Ashman and Dr. Prasad Shastri. This study used the polymers as presently defined in the '442 application, using chemical and light hardening. The study was described as Example 48 in related application Ser. No. 11/240,747 (U.S. 2006/005247; Exhibit K), a continuation-in-part of the present application.

32. The pilot study used the anhydride polymers as described in the '442 application. The polymers were hardened using both light and chemical curing. Placement and mixing was done using the same protocol as described in the Brooks study. Additionally, rabbits unused in the Brooks study were used in the Yukna Pilot study. The histology data from this study is provided in Exhibit J.

33. According to the '247 Application, the samples used in Example 48 were as follows:

F1 - 90 % MCPP (methacrylated carboxyphenoxypropane) and 10% MSA (methacrylated sebacic acid) in a semi-interpenetrating network.
F2 - 90% MCPP and 10% MSA ; formulated with 10% Bioplant® HTR® and $CaCO_3$
F3 - 90% MCPP and 10% MSA ; formulated with 25% Bioplant® HTR® and $CaCO_3$
F4 - 100% MSA; formulated with 25% Bioplant® HTR®

The chemical initiators were camphorquinone and ethyl 4-dimethylaminobenzoate.

34. My understanding of the study is that that 6 mm trephine bur was used to create defects in the tibia and zygoma. Each defect was grafted with one of the test compounds or left alone as an ungrafted control. This was described previously in Exhibit H.

35. The compounds were cured for less than one minute with a light cure and were chemically cured as well. The rabbits were killed at the end of 4 and 8 weeks after grafting, and histological analysis was done of block tissue samples.

36. Exemplary histologies of tibia defects at 8 weeks are shown in Exhibit J. Slide 1 demonstrates Bioplant® HTR® in the anhydride polymer in a tibia having gross specimen defects. There is regeneration of new bone (4), no inflammation, adhesion to defect walls (2). Slide 2 shows the new bone formation around an HTR particle (1&2). Slide 3 shows new bone formation on the Bioplant® HTR® particles (2). Slide 4 shows the new bone formation at the interface of Bioplant® HTR® particles (1), new bone(2), and a resorption area of the anhydride and CaCO3. Slides 5 – 8 are histologies of polymers not containing HTR particles.

37. Based on the results of the Yukna study, it is my opinion that a curable composition of the polymers as described in the '442 application and used in the study well as a bone implant material and have good clinical osseointegration..

Analysis

38. In my opinion, a comparison between the Huys study and the Yukna study provides substantial evidence that a combination of the Schacht polymer with a bone substitute does not provide a viable bone implant material, whereas the combination of a polymer and bone substitute as claimed in the '442 application provides a viable bone implant material which promotes regeneration of new bone, little to no inflammation and is load bearing.

39. Further, it is my opinion that a person of ordinary skill in polymer chemistry in the dental implant field would have no reason or motivation to modify the polymers as described by Schacht in such a way as to provide a polymer with all the limitations of the invention claimed in the '442 patent application.

40. I further declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. I further declare that these statements are made with the knowledge that the willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States code, and that such willful false statements may jeopardize the validity of the instant application or of any patent issued thereupon.

Respectfully submitted,

List of Exhibits

A	Dr. Langer C.V.
B	In Vivo Tests Details
C	Chart of Sheep tests, 30 Days post Op
D	Huys Sheep # 0767, including 5 images
E	Huys Sheep # 4562, including 2 images
F	Huys Sheep # 5261, including 4 images
G	Huys Sheep # 0577, including 4 images
H	Study Proposal for Brooks study
I	Thesis of MaryAnn Brooks
J	Histology of tibia defects at 8 weeks – 8 images
K	U.S.Pat. Pub. 2006/005247

Dr. Robert S. Langer _____

Date 6/30/07

EXHIBIT A

ROBERT SAMUEL LANGER

Curriculum Vitae

DATE & PLACE OF BIRTH August 29, 1948, Albany, New York

EDUCATION

1974 Sc.D., Chemical Engineering, MIT
1970 B.S. (with distinction) Chemical Engineering, Cornell University

HONORS

2007 Herman F. Mark Award (American Chemical Society, Polymer Chemistry Division)
2007 Chemistry of Materials Award (American Chemical Society)
2007 Honorary Doctorate (Yale University)
2007 Annual Findling Lecturer (Mayo Clinic)
2007 W.M. Keck Distinguished Lecturer (Lehigh University)
2007 Alexander Rich Lecturer (Massachusetts Institute of Technology)
2007 William Shucart Lecturer (Tufts University)
2007 Ford Lecturer (Case Western University)
2006 Elected to the National Inventors Hall of Fame
2006 Honorary Doctorate (Northwestern University)
2006 Honorary Doctorate/Commencement Address (Albany Medical College)
2006 Bailey Award (American Institute of Chemical Engineers)
2006 Distinguished Lecturer (University of Pennsylvania School of Medicine)
2006 Weiss Lecturer (Northeastern University)
2005 Von Hippel Award (Materials Research Society)
2005 Albany Medical Center Prize in Medicine and Biomedical Research
2005 Dan David Prize (Materials Science)
2005 Honorary Doctorate (Uppsala University)
2005 Honorary Doctorate/Commencement Address (Pennsylvania State University)
2005 Honorary Doctorate (University of Nottingham)
2005 Lifetime Achievement Award (Society for In Vitro Biology)
2005 Rainer Hoffmann Product through Science Award (Controlled Release Society)
2005 Hodgins Lectureship (McMaster University)
2005 Technology Innovation and Development Award (Society of Biomaterials)
2005 Washington Award (Western Society of Engineers)
2005 John and Donna Hall Lectureship (Vanderbilt University)
2005 Keewaunee Lecturer (Duke University)
2005 Gavel Clinical Research Lecturer (The Forsyth Institute)
2005 Talamo Lecturer (Harvard Medical School)
2004 Charles F. Kettering Prize (General Motors Cancer Research Foundation)
2004 Presidential Lecturer (University of Texas Health Science Center, San Antonio)
2004 Pirkey Lectureship in Chemical Engineering (University of Texas, Austin)
2004 Evans Memorial Award Lectureship (Ohio State University)
2004 Nelson Taylor Award (Pennsylvania State University)
2004 Benjamin Zweifach Distinguished Lecturer (City College of New York)
2004 Nelson Leonard Lecturer (University of Illinois)
2004 Donald Katz Lecturer (University of Michigan)
2003 Heinz Award for Technology, Economy and Employment
2003 Harvey Prize in Science and Technology and Human Health
2003 John Fritz Medal (American Association of Engineering Societies)
2003 Founders Lecturer (University of Wisconsin)
2003 Rohm and Hass Lecturer (Stanford University)
2003 Elected to the Academy of Achievement (Golden Plate Award)

2003 Tripathy Endowed Memorial Lecture (University of Massachusetts, Lowell)
2003 Skinner Memorial Lecture (Northwestern University)
2003 Honorary Doctorate (University of Liverpool, England)
2003 Maurice and Yetta Glicksman Lecturer (Brown University)
2003 FMC Lecturer (Princeton University)
2003 Seymour J. Kreshover Lecturer (National Institutes of Health)
2003 Whitaker Lecturer (American Society of Artificial Organs)
2002 Dickson Prize for Science (Carnegie Mellon University)
2002 Charles Stark Draper Award (National Academy of Engineering)
2002 Othmer Gold Medal (Chemical Heritage Foundation)
2002 Nagai Innovation Award (Controlled Release Society)
2002 Feigenbaum - Levine Lecturer (Beth Israel Hospital at Harvard Medical School)
2002 Honorary Doctorate (Hebrew University of Jerusalem)
2002 Herman Schwan Award (University of Pennsylvania)
2002 Distinguished Lecturer (University of Louisville)
2002 Institute Lecturer (American Institute of Chemical Engineers)
2001 Harrison Howe Award (American Chemical Society)
2001 Ullyot Lecturer (Chemical Heritage Foundation)
2001 Clapp Lecturer (Brown University)
2001 Julian Smith Lecturer (Cornell University)
2001 Mason Lecturer (Stanford University)
2001 Distinguished Lecturer (Carnegie Mellon)
2000 Herman Beerman Lecturer (Society for Investigative Dermatology)
2000 Millennial Lecturer (University of Liverpool)
2000 Bayer Lecture (University of Pittsburgh)
2000 Bayer Stein Honorary Lecture (University of Massachusetts at Amherst)
2000 Honorary Doctorate (The Catholic University of Louvain, Belgium)
2000 Glaxo Wellcome International Achievement Award (Royal Pharmaceutical Society of Great Britain)
2000 Millennial Pharmaceutical Scientist Award (Millennial World Congress of Pharmaceutical Sciences)
2000 William G. Lowrie Lectureship (The Ohio State University)
2000 Frank T. Gucker Lecturer (Indiana University)
2000 First Pierre Galletti Award (American Institute of Medicine & Biological Engineering)
2000 First Patten Distinguished Lectureship (University of Colorado at Boulder)
2000 Wallace Carothers Award (American Chemical Society, Delaware Section)
1999 American Chemical Society Award in Polymer Chemistry
1999 Esselen Award (American Chemical Society, Northeast Section)
1999 G.N. Lewis Medal and Lecturer (University of California at Berkeley)
1999 Beckman Lecturer (University of Illinois at Urbana)
1999 Reilly Lecturership (Notre Dame University)
1999 Ebert Prize (American Pharmaceutical Association)
1998 Outstanding Pharmaceutical Paper Award (Controlled Release Society)
1998 Lemelson-MIT Prize for Invention and Innovation
1998 The Nagai Foundation Tokyo International Prize
1998 Wagner Lectureship (University of Michigan)
1998 Ewing Halsell Foundation Lectureship (University of Texas Health Center, San Antonio)
1998 Robert R. Linton Distinguished Lecture; New England Society for Vascular Surgery
1998 Marcus Memorial Lecturer (Washington University, St. Louis)
1998 Joseph Stokes, Jr. Lectureship (University of Pennsylvania)
1997 Killian Faculty Achievement Award (MIT)
1997 Wiley Medal (U.S. Food and Drug Administration)
1997 Honorary Doctorate (The Technion - Israel)
1997 William J. Rashkind Memorial Lecture (American Heart Association)
1997 Rohm and Haas Lecturer in Materials Chemistry (University of North Carolina)

1996 Gairdner Foundation International Award
1996 Honorary Doctorate (Eidgenossische Technische Hochschule-ETH, Switzerland)
1996 William Walker Award (American Institute of Chemical Engineers)
1996 Society of Plastics Engineers International Award
1996 Ebert Prize (American Pharmaceutical Association)
1996 Elected a Fellow of Biomaterials Science and Engineering
1996 The Berkeley Lecturer (University of California, Berkeley)
1996 Avis Distinguished Visiting Professor (University of Tennessee)
1995 International John W. Hyatt Service to Mankind Award (Society of Plastics Engineers)
1995 Ebert Prize (American Pharmaceutical Association)
1995 Distinguished Medical Scientist Lecturer (Ohio State University)
1995 Lacy Lecturer (California Institute of Technology
1995 Ralph Peck Memorial Lecturer (Illinois Institute of Technology)
1995 Elected a Fellow (American Association of Pharmaceutical Scientists)
1995 PEL Associates Award (PEL Associates, Groton, Connecticut)
1994 Whitaker Distinguished Lecturer (Biomedical Engineering Society)
1994 Elected to the American Academy of Arts and Sciences
1994 Elected a Fellow, Society of Biomaterials
1994 Miles Lecturer (Cornell University)
1994 Feigenbaum Memorial Lecturer (Beth Israel Hospital, Harvard Medical School)
1993 Distinguished Pharmac. Scientist Award (Highest Honor of the Amer. Assoc.of Pharm.Scient.)
1993 Kurt Wohl Memorial Lecturer (University of Delaware)
1993 Priestley Lecturer (Penn State University)
1992 Elected to the National Academy of Sciences
1992 Elected to the National Academy of Engineering
1992 American Chemical Society Award for Applied Polymer Science (Phillips Award)
1992 Perlman Memorial Award Lecturer (American Chemical Society, Biochemical Technology Division)
1992 Elected a Founding Fellow, American Institute of Medical and Biological Engineering
1992 Kelly Distinguished Lecturer (Purdue University)
1992 Miles Distinguished Lecturer (University of Pittsburgh)
1992 Outstanding Pharmaceutical Paper Award (Controlled Release Society)
1991 Organon Teknika Award (European Society for Artificial Organs)
1991 Charles M.A. Stine Award in Materials Science and Eng. (Am. Institute of Chem.Eng.)
1991 Louis W. Busse Lecturer (University of Wisconsin)
1991 Sidney Riegelman Lecturer (University of California, San Francisco)
1991 Ashton-Cary Lecturer (Georgia Institute of Technology)
1991 Sandoz-Dorsey Lecturer (Ohio State University)
1990 Professional Progress Award (American Institute of Chemical Engineers)
1990 Clemson Award for Basic Research (Society for Biomaterials)
1990 Outstanding Pharmaceutical Paper Award (Controlled Release Society)
1989 Elected to the Institute of Medicine of the National Academy of Sciences
1989 Creative Polymer Chemistry Award (American Chemical Society, Polymer Division)
1989 Outstanding patent in Massachusetts and one of the twenty outstanding patents in the U.S. (Intellectual Property Owners, Inc.)
1989 Founders Award for Outstanding Research (Controlled Release Society)
1989 Walter F. Enz Lecturer (University of Kansas)
1988 Elected to the Gordon Conference Research Council
1988 Elected Chairman, Gordon Conference on Drug Carriers in Biology and Medicine
1988 Robert Rushmer Lecturer (University of Washington, Seattle)
1988 1st Presidential Lecturer, Controlled Release Society (Basel, Switzerland)
1987 Biomedical Research Council Lecturer (University of Michigan)
1986 Food, Pharmaceutical and Bioengineering Award (American Institute of Chemical Engineers)
1986 Elmer L. Linseth Lecturer (Case Western Reserve University)

1983 Outstanding Paper, Institute of Electrical and Electronic Engineering
1983 Merck, Sharpe and Dohme Lecturer (University of Puerto Rico)
1982 Paper Listed as One of the Outstanding Papers of the Year, CHEMTECH
1982 Recipient of the first Dorothy W. Poitras Chair, MIT
1982 Outstanding Teacher Award, MIT Graduate Student Council

EMPLOYMENT

2/05-present	Institute Professor, Massachusetts Institute of Technology
7/88-1/05	Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering, MIT Department of Chemical Engineering; Whitaker College of Health Sciences, Technology, and Management; and the Harvard-MIT Division of Health Sciences and Technology
7/99-present	Senior Lecturer on Surgery, Harvard University, Harvard Medical School
7/85-6/88	Professor of Biochemical Engineering, MIT, Department of Applied Biological Sciences, Whitaker College of Health Sciences, Technology, and Management, and the Harvard-MIT Division of Health Sciences and Technology
7/81-6/85	Associate Professor of Biochemical Engineering, MIT, Department of Nutrition and Food Sciences and the Whitaker College of Health Sciences Technology, and Management, and the Harvard-MIT Division of Health Sciences and Technology
7/78-6/81	Assistant Professor of Nutritional Biochemistry, MIT, Department of Nutrition and Food Sciences
7/77-6/78	Assistant Professor of Nutritional Biochemistry, MIT (Visiting), Department of Nutrition & Food Sciences
7/74-present	Research Associate, Children's Hospital Medical Center, Harvard Med. School, Boston, MA
9/72-6/74	Research Assistant, MIT
9/72-8/73	Chairman, Math and Science Departments, The Group School, Cambridge, MA

PROFESSIONAL AND ACADEMIC ORGANIZATIONS

Controlled Release Society (Elected President, 1991-1992) (Elected to Board of Governors, 1981-1985; Chairman, Regulatory Affairs Committee, 1985-1989).
Biomedical Engineering Society (Elected to the Board of Directors, 1991-1994)
American Institute of Chemical Engineers (Food, Pharmaceutical and Bioeng. Division)
American Chemical Society (Polymer Division)
American Society of Artificial Internal Organs (Program Committee 1984-1987; Membership Committee (1991-93)
International Society of Artificial Internal Organs
Scientific Advisory Board, Department of Chemical Engineering, Georgia Institute of Technology (1992-2000)
Society for Biomaterials (Elected a Fellow, 1994)
American Association of Pharmaceutical Scientists (Elected a Fellow, 1995)
American Institute of Medical and Biological Engineers (Elected Founding Fellow, 1992; Elected Chair, College of Fellows, 1995)
The Science Board, the United States Food and Drug Administration (FDA) (highest Advisory Board of the FDA), 1995--2002 (Chair from 1999 -- 2002)
Scientific Advisory Board, Schepens Eye Institute, Harvard Medical School (1995-1998)
Board of Scientific Counselors, National Institutes of Health Center for Research Resources (1996-2001)
Scientific Advisory Board, Division of Chemistry and Chemical Engineering, California Institute of Technology (1999-)
Scientific Advisory Board, Department of Chemical Engineering, Princeton University (1999-)
Board of Overseers, Othmer Research Institute, Brooklyn Polytechnic Institute (2001-)
Board of Directors, McGovern Institute, Massachusetts Institute of Technology (2001-)
Board of Directors, Whitehead Institute (2003-)
Chair, Killian Award Committee (2004)

COURSES TAUGHT

20.002U	(1977 - 1988)	Laboratory in Applied Biology
20.S35	(1979 - 1988)	Pharmacological Engineering
20.11G	(1979 - 1988)	Analytical Practices in Biochemistry
HST 110	(1979 - 1981)	Renal Pathophysiology

20.113	(1987 - 1988)	Problems in Biotechnology
10.02J	(1989 -)	Biotechnology and Engineering
10.361	(1989 -)	Integrated Chemical Engineering
10.13	(1989 -1991)	Thermodynamics
10.984	(1990 -)	Biomedical Applications of Chemical Engineering
10.26	(1992 -)	Senior Chemical Engineering Project Laboratory

MIT ACTIVITIES

1972-73, 80-	Board of Trustees, MIT Community Service Fund
1972-74	Committee on Preprofessional Advising and Education, MIT
1972-74	Steering Committee, Urban Action, MIT
1977-85	Freshman Advisor
1978-	Undergraduate Advisor
1980-	Premedical Advisory Council, MIT
1977-80	Seminar Committee, Department of Applied Biological Sciences, MIT
1978-80	Asinari Committee, MIT
1979-88	Undergraduate Affairs Committee, Department of Applied Biological Sciences, MIT (Chairman, 1981-1985)
1980-84	MIT-Wellesley Upward Bound Joint Steering Committee
1981-82, 84-85	Financial Aid Committee, Department of Applied Biological Sciences, MIT
1981-86	Admissions Committee, Harvard-MIT Division of Health Sciences and Technology
1983-87	Curriculum Committee, Dept. of Applied Biological Sciences (Chairman, 1985-1987)
1983-87	Radiation Committee, MIT
1983-97	Sea Grant Committee, MIT (Chairman, 1993-1997)
1985-87	Admissions Committee, Harvard MD-POD Program
1986-92	Admissions Committee, MIT Medical Engineering-Medical Physics Program
1986-	Harvard-MIT Joint Committee on Health Sciences and Technology
1988	Search Committee for Department Head, Department of Chemical Engineering
1988-1992	Admissions Committee, Department of Chemical Engineering
1989-1991	Undergraduate Committee, Department of Chemical Engineering
1991-1993	Seminar Chairman, Department of Chemical Engineering
1993-	Board of Advisors, MIT Industrial Summer Session Program
1994-1995	Selection Committee for Co-Director of Harvard-MIT HST Program
2000-	Harvard-MIT Division of Health Sciences and Technology Advisory Council

EDITORIAL BOARDS

1983-2002	BIOMATERIALS- Editor
1987-	BIOMATERIALS, ARTIFICIAL CELLS, AND IMMOBILIZATION TECHNOLOGY (Associate Editor, 1991-)
1983-92	SELECTIVE CANCER THERAPEUTICS (CANCER DRUG DELIVERY)
1983	METHODS OF ENZYMOLOGY-DRUG DELIVERY SYSTEMS
1984-98	JOURNAL OF CONTROLLED RELEASE
1985-	BIOMEDICAL POLYMERS
1986-	ADVANCED DRUG DELIVERY SYSTEMS
1987-	DRUG DESIGN AND DELIVERY
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1992-	INTERNATIONAL JOURNAL OF DRUG TARGETING
1992-	JOURNAL OF BIOACTIVE AND COMPATIBLE POLYMERS
1994-98	CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS

1994-	JOURNAL OF PHARMACEUTICAL SCIENCE
1995-	TISSUE ENGINEERING
1995-	THE ENCYCLOPEDIA OF CONTROLLED DRUG DELIVERY
1996-	BIRKHAUSER: SYNTHETIC BIODEGRADABLE POLYMER SCAFFOLDS
1996-98	CHEMICAL AND ENGINEERING NEWS
1997-99	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES
1997-	ANNUAL REVIEWS OF BIOMEDICAL ENGINEERING
1997-	BIOMEDICAL MICRODEVICES
1998-	DIABETES TECHNOLOGY & THERAPEUTICS
1999-	JOURNAL OF POLYMER SCIENCE, CHEMISTRY
1999-	PHARMACEUTICAL SCIENCE
1999-	REGENERATIVE MEDICINE
1999-	METHODS OF TISSUE ENGINEERING
1999-	ANGEWANDTE CHEMIE
2000-	EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES
2002-	JOURNAL OF INVESTIGATIVE DERMATOLOGY-Associate Editor
2004-	MECHANICS AND CHEMISTRY OF BIOSYSTEMS
2006-	JOURNAL OF BIOPHARMACEUTICS AND BIOTECHNOLOGY
2006-	AMERICAN CHEMICAL SOCIETY-Editorial Advisory Board of Bioconjugate Chemistry
2006-	BIOCONJUGATE CHEMISTRY
2006-	BIOMACROMOLECULES
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EXHIBIT B

IN VIVO TESTS BIORESORBABLE POLYMERS IN SHEEP

Animals

7 female sheep, age 3 – 5 years (mature dentition)

Aim

Immediate fixation of titanium implants after extraction of molars by using a combination of Bioplant® HTR-24 and a new bioresorbable light curing polymer (HTR-LC: Bioplant® Hard Tissue Replacement – Light Cured). This investigation will study the bone ingrowth in the extraction socket and around the implants, as well as in the new polymer. The efficacy of using Platelet Rich Plasma (PRP) will also be investigated.

Method – Time frame

Day –14
Arrival of the sheep at the Veterinary Faculty
Control of general health and dentition + medication (de-vermification) if necessary

Day –2
Pre-op intra oral Rx of the teeth that will be removed
Conventional Rx of the mandible: lateral and oblique

Day –1
Stop feeding. Prophylactic AB (Excenel® RTU) + NSAID (Finadyne®)

Day 0
Extraction P3 and P4 from left and right mandible
Left:

- two titanium implants (Ankylos®), one normal and one modified (square neck) in one socket, other socket no implants
- Bioplant® HTR-24, mixed with Platelets Rich Plasma (PRP) around the implants and in the socket without implants
- around the neck of the implants and in the occlusal part of the socket without implants: combination Bioplant® HTR-24/LC .

Right:

- two titanium implants (Ankylos®), one normal and one modified (square neck) in one socket, other socket no implants
- Bioplant® HTR-24, mixed with marrow bleeding, around the implants and in the socket without implants
- around the neck of the implants and in the occlusal part of the socket without implants: combination Bioplant® HTR-24/LC polymer

Medication preoperative: AB (Excenel® RTU) and Methylprednisolon 0.5mg/kg IM

Postoperative Rx: conventional, intra-oral and CT-scan

Day +1
AB (Excenel® RTU, 1mg/kg)

Day +2
AB (Excenel® RTU, 1mg/kg)

Day +3
AB (Excenel® RTU, 1mg/kg)

Day +30
Rx: conventional + intra-oral

Day +90
Rx: conventional + intra-oral

Day +180
Euthanasia
Rx: conventional, intra-oral and CT-scan
Biopsies for histology

Practical details: (DOGS)

The accommodation and the care of the sheep will be done by the Dept. for Anesthesia and Surgery.
The anesthesia itself will be done by Prof. Gasthuys and Dr. Vlaminck.
The surgery itself will be performed by Dr. Huys and one of his assistants. Digital foto's will be taken during the surgery, done by someone of the above mentioned Dept.
Conventional Rx and CT-scan will be taken by Dr. Saunders. Intra-oral Rx will be taken by Dr. Verhaert.
The eventual possibility for SEM pictures will be asked by Prof. Schacht to Prof. Simoens.

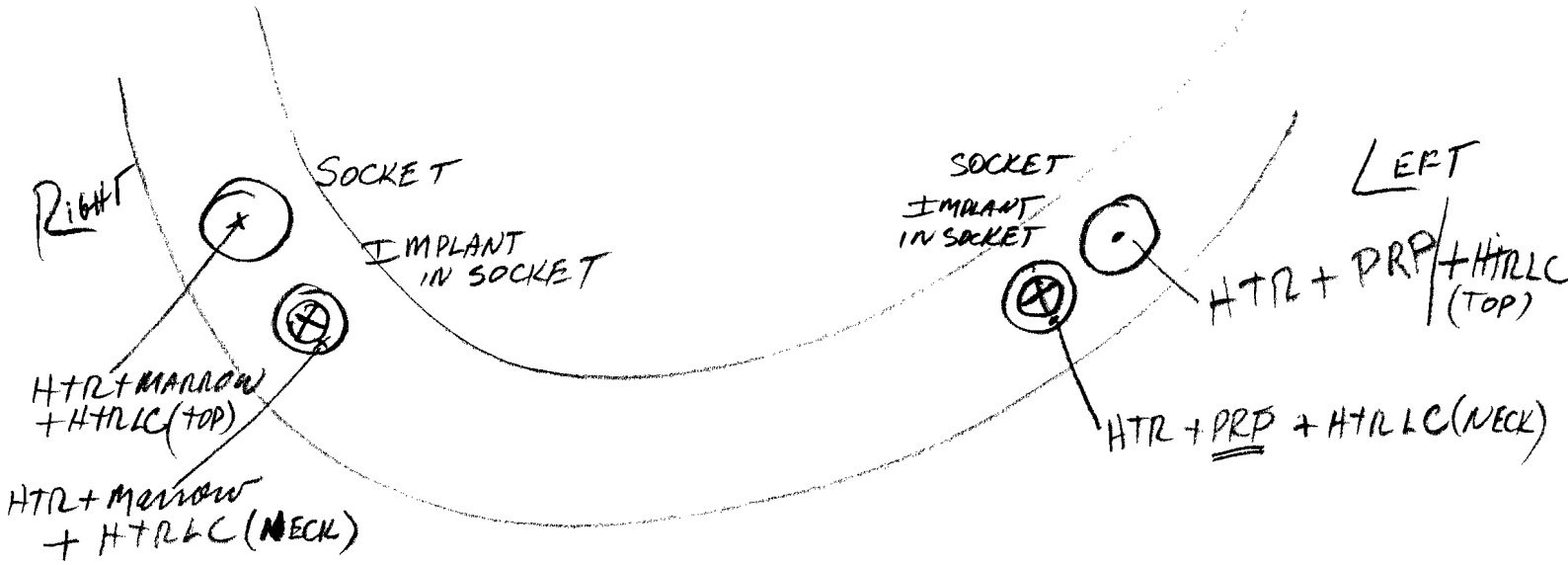


EXHIBIT C

DEFECT = LOST IMPLANT

SHEEP TESTS 30 DAYS POST-OP

		Tooth	Implant (TYPE)	PRP	Polym. Time	Healing	Implant lost
Sheep 1	L	P2	A11	No	80	Yes	No
		P3	A11	No	80	Defect	Yes ✓
	R	P2	A11	Yes	80	Yes	No
		P3	A11	Yes	80	Yes	No
Sheep 2	L	P2/P3	B11	No	80	Defect	Yes ✓
	R	P2/P3	A11	Yes	80	Yes	No
Sheep 3	L	P2	A11	No	80	Yes	No
		P3	A11	No	80	Yes	No
	R	P2	A11	Yes	80	Defect	Yes ✓
		P3	A11	Yes	80	Yes	No
Sheep 4	L	P2/P3	B11	No	120	Defect	Yes ✓
	R	P2/P3	B11	Yes	140	Yes	No
Sheep 5	L	P2/P3	B11	No	120	Defect	Yes ✓
	R	P2/P3	A11	Yes	120	Yes	No
Sheep 6	L	P2	A11	No	80	Yes	No
		P3	A11	No	80	Yes	No
	R	P2	A11	Yes	80	Yes	No
		P3	A11	Yes	80	Defect	Yes ✓
Sheep 7	L	P2	A9.5	No	80	Yes	No
		P3	A14	No	80	Yes	No
	R	P2	A11	Yes	80	Yes	No
		P3	A9.5	Yes	80	Defect	Yes ✓

NOTE: ALL IMPLANTS EITHER LOST OR FAILING

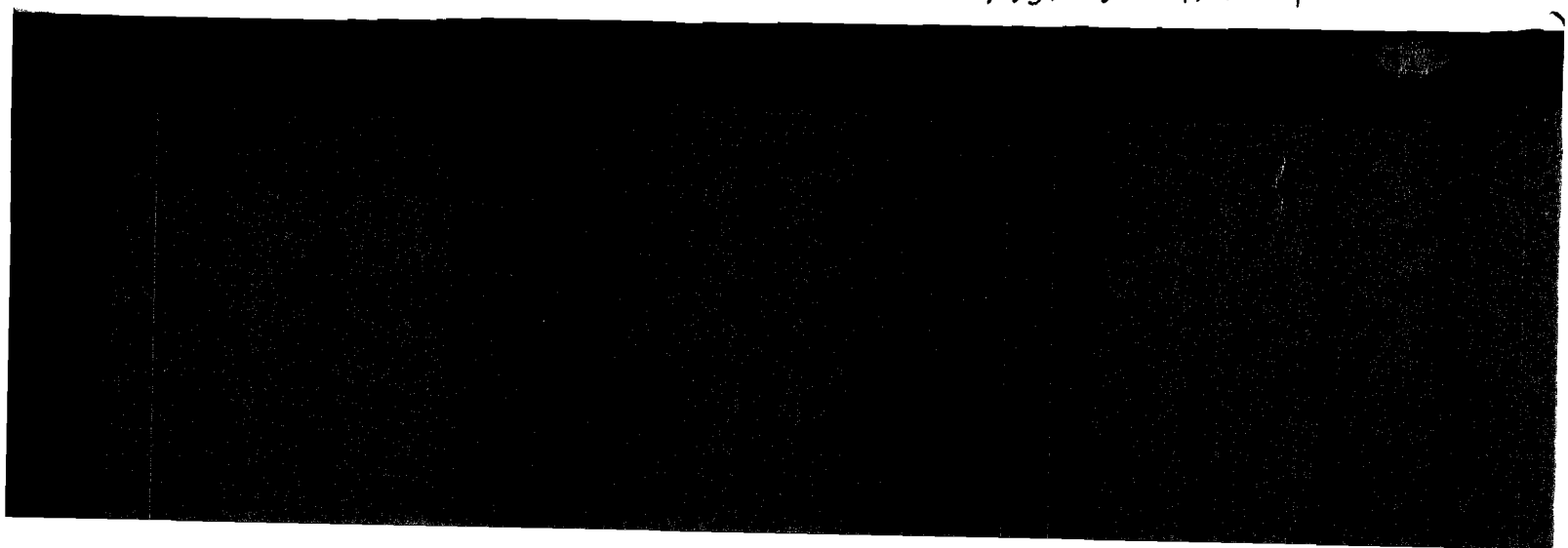
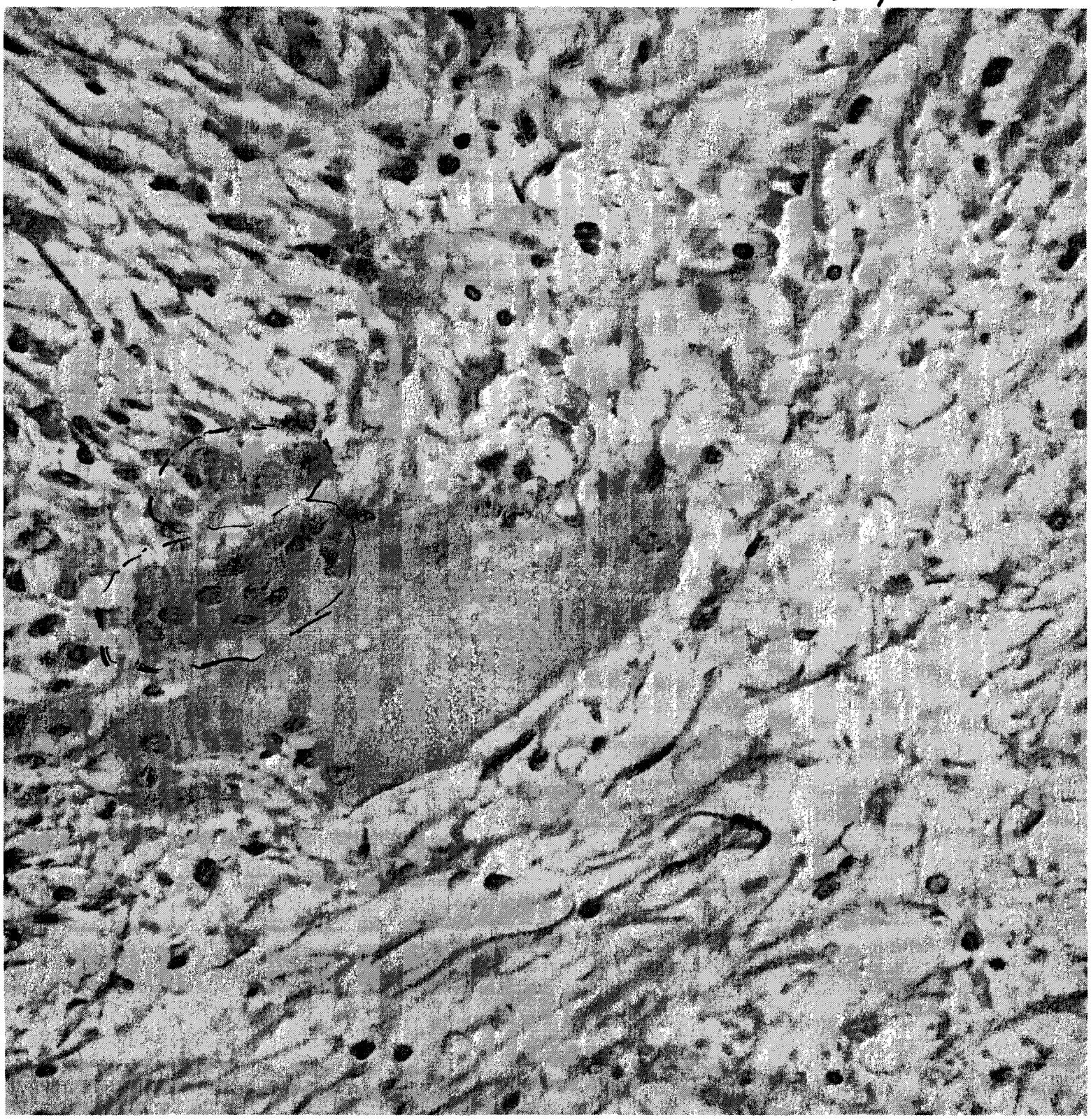


EXHIBIT D

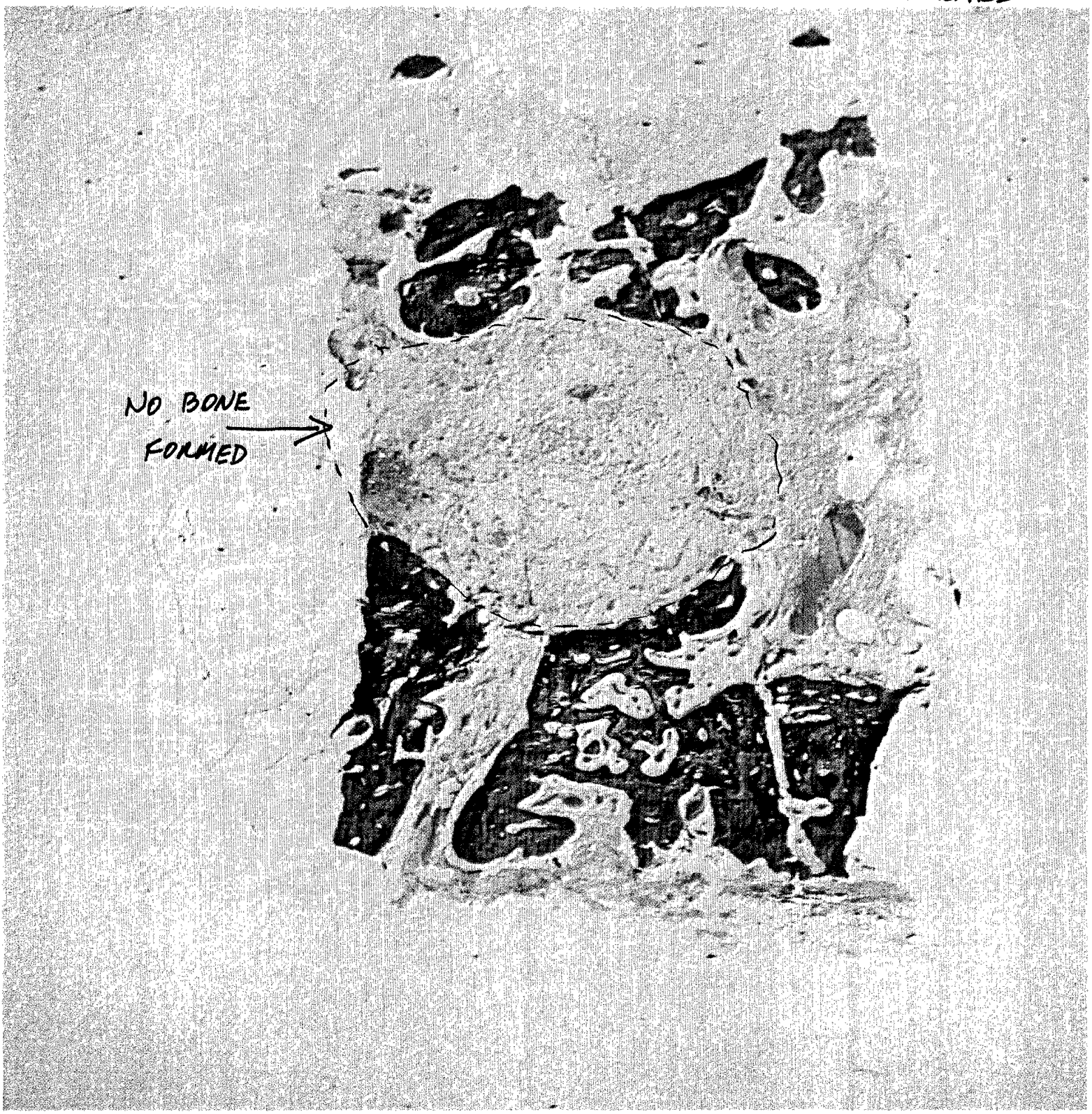
SHEEP #0767

POOR BONE FORMATION / GIANT CELLS

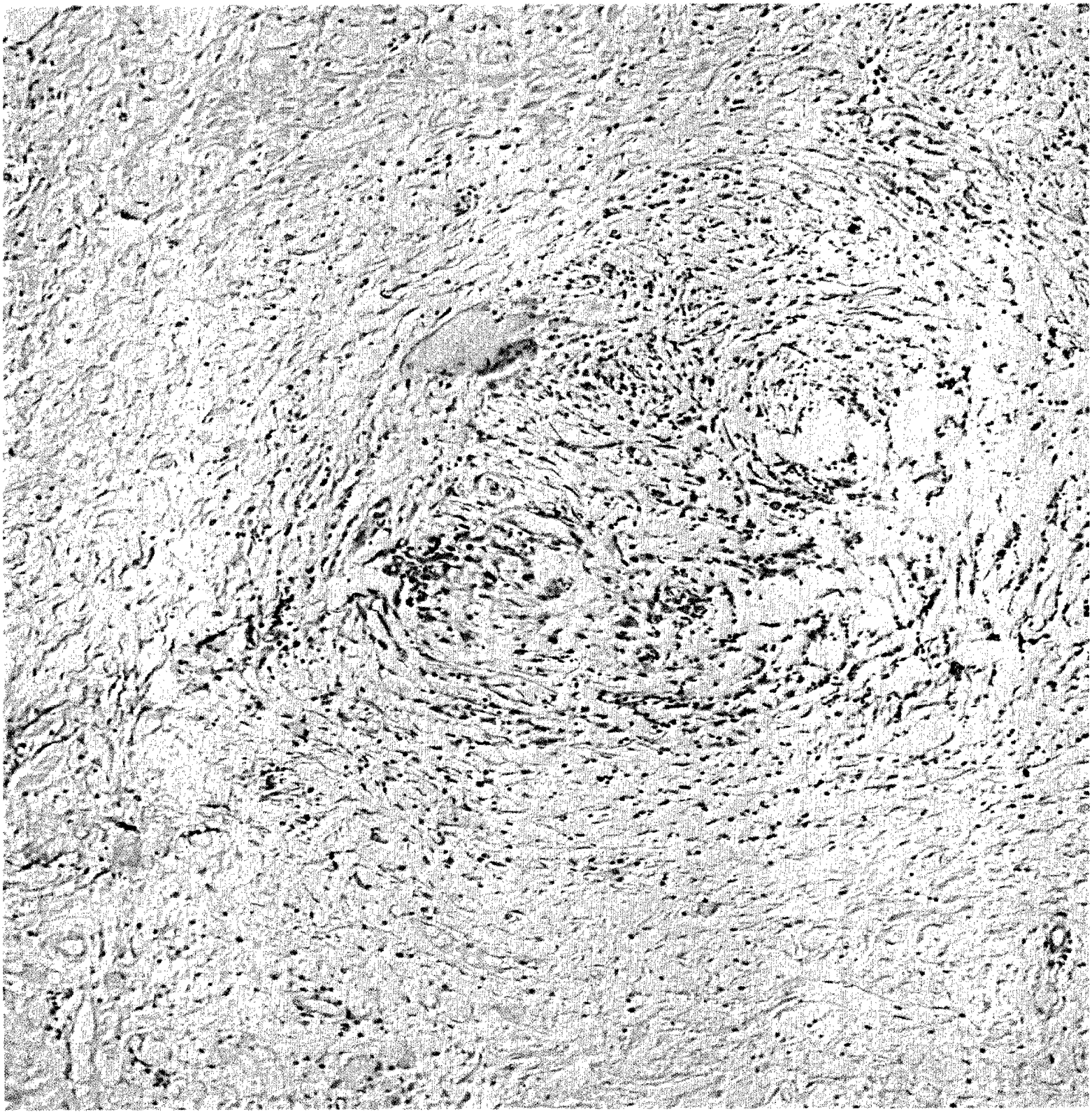


0167

EXTRACTION SOCKET — NO BONE FORMED

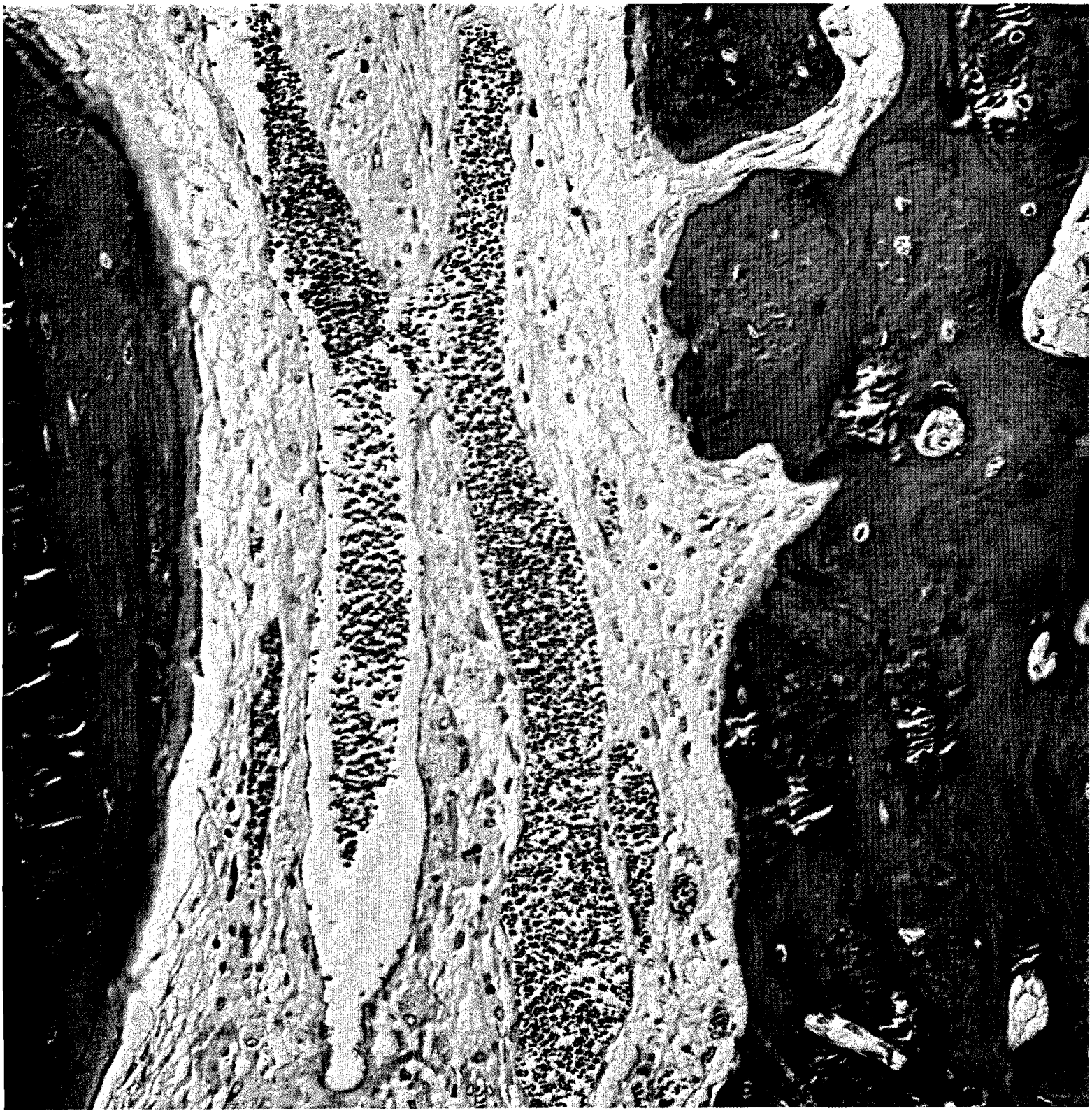


0767
GIANT CELLS/LITTLE BONE
DENSE CONNECTIVE TISSUE



#0767

IMPLANT LOST



#0767

DENSE FIBROUS REACTION AROUND GRAFT MATERIAL

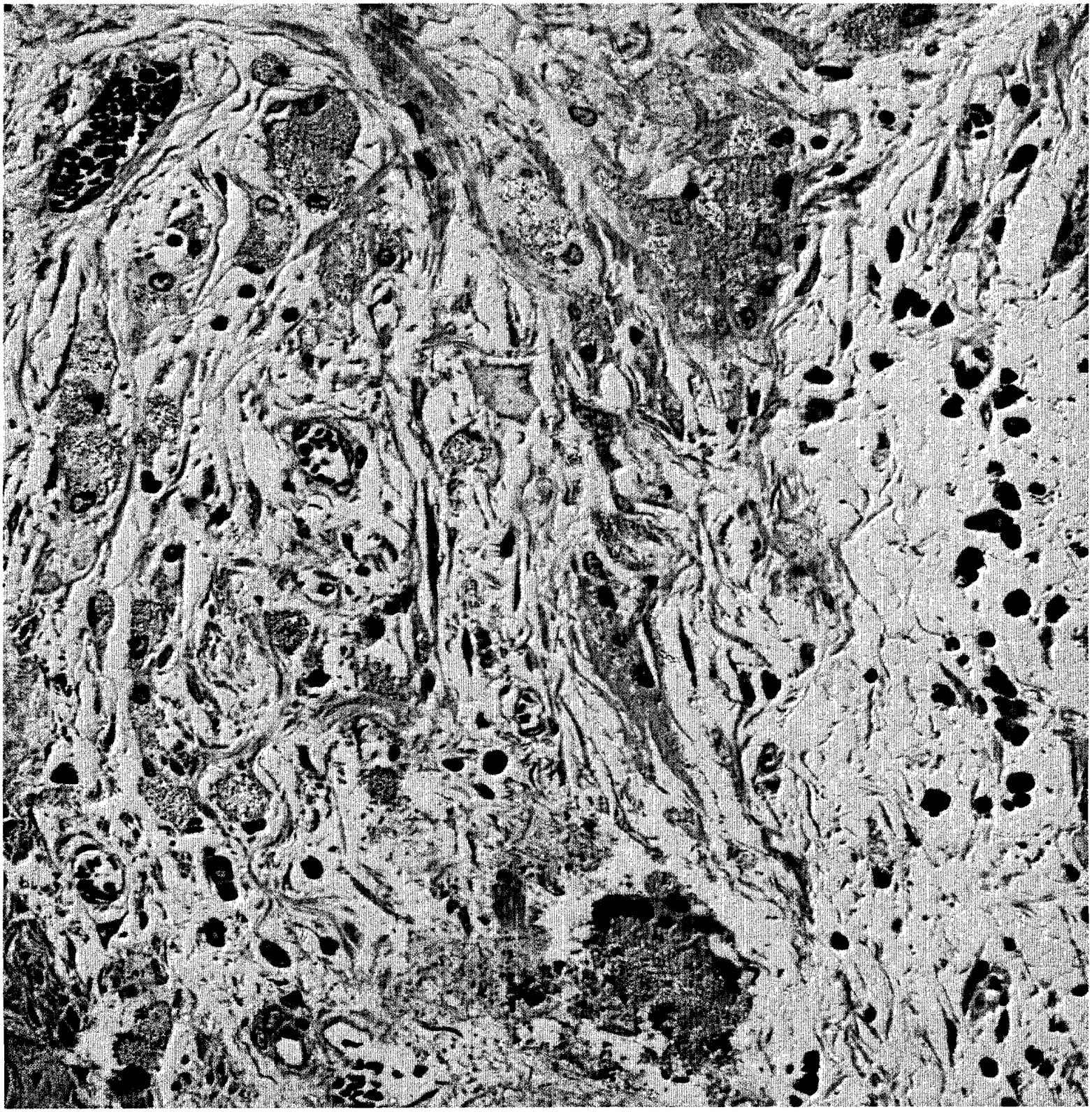
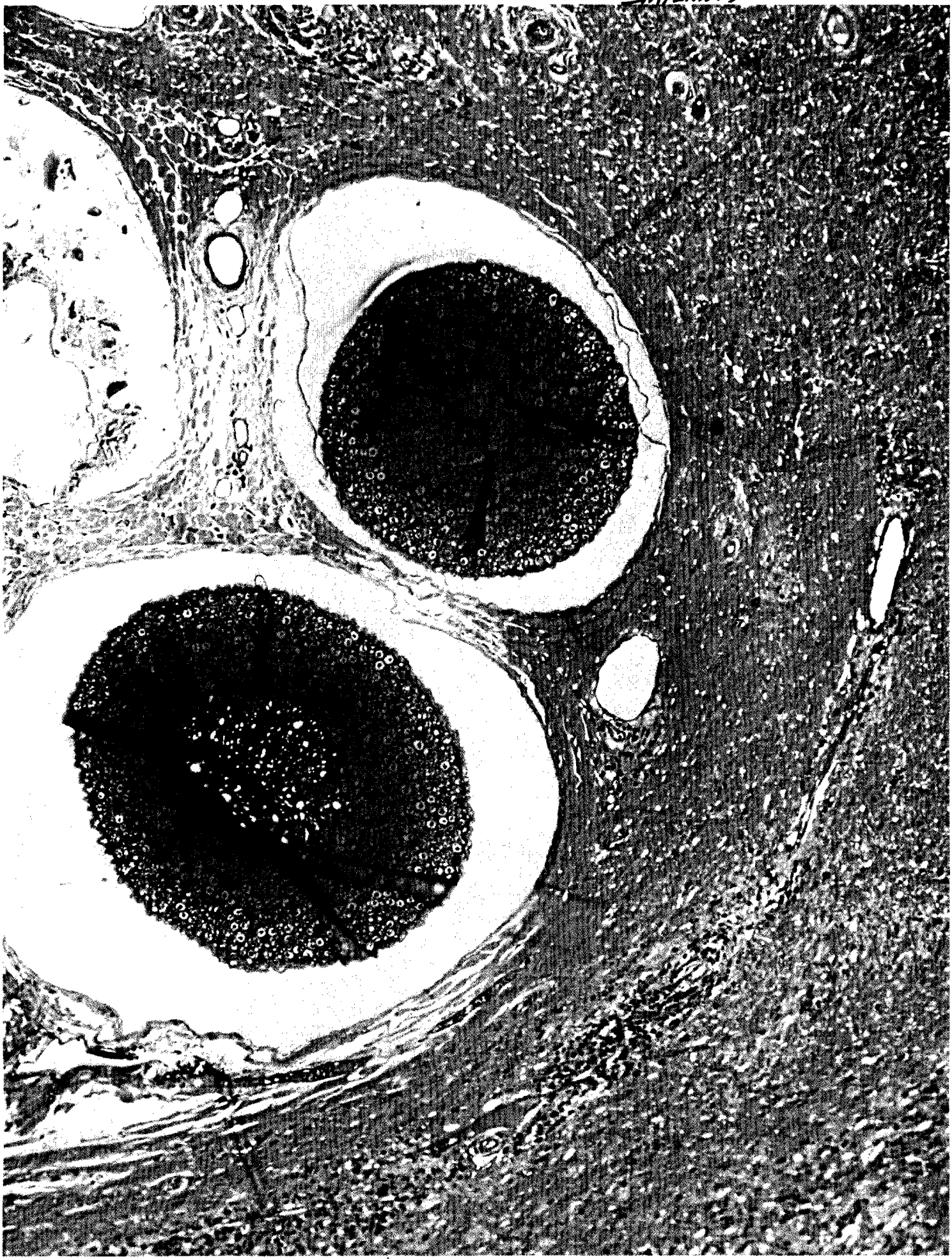


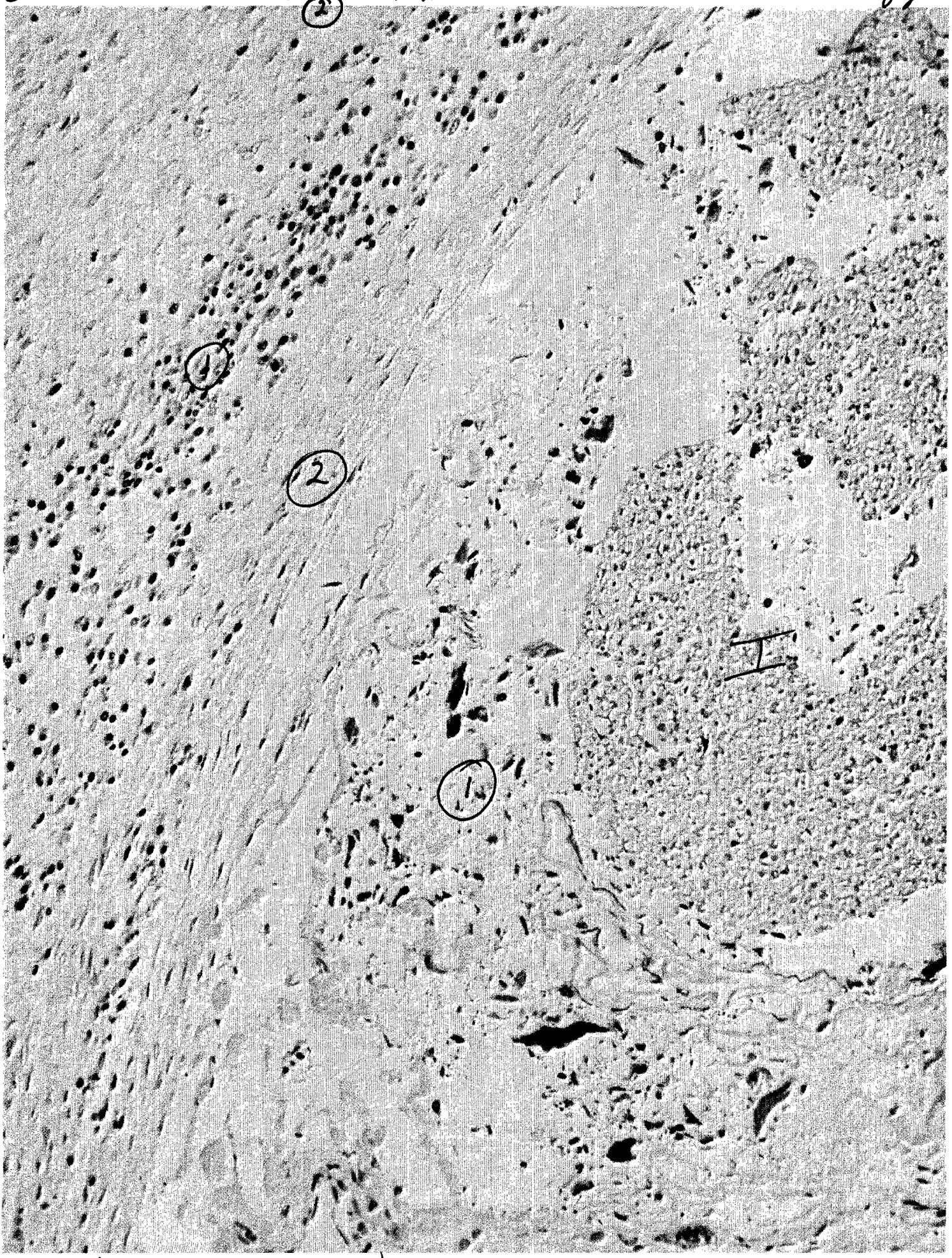
EXHIBIT E

CHRONIC INFLAM. AND ENCAPSULATION / FAILURE 2 SOCKET IMPLANTS # 4562 FIG 1



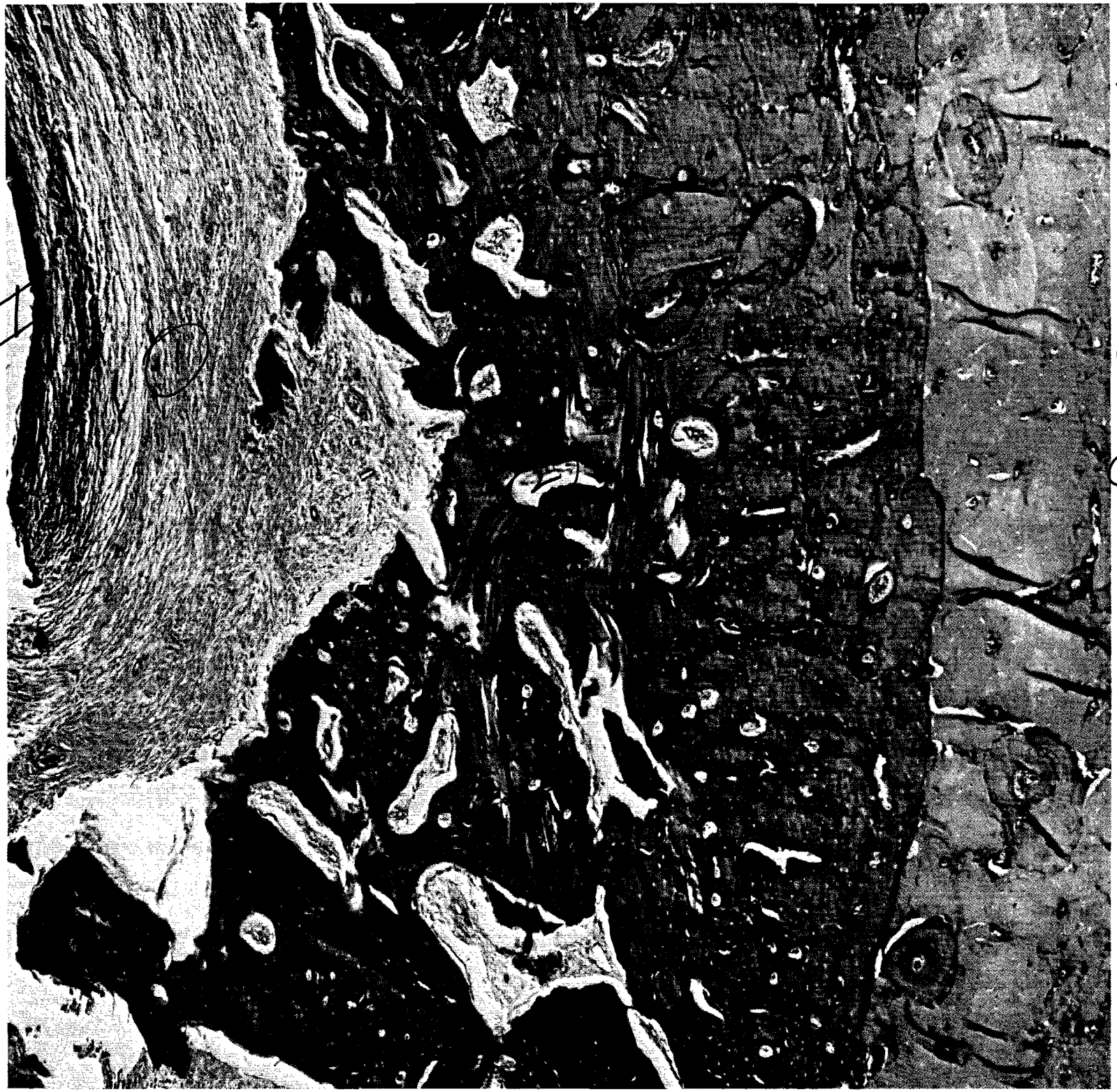
NO BONE FORMATION

(-t) CHRONIC INFLAMMATION/C.T. MEMBRANE AROUND IMPLANT #4562 fig 2



NO BONE FORMATION

EXHIBIT F



5261

TITANIUM IMPLANT apical 1/3 of Impl.

DENSE FIBROUS TISSUE (1)

SOME NEW BONE (2)

FIG. 1

#5261 pg 2

IMPLANT FAILURE
EPITHILUM LINING
DENSE INFLAMATION

I

#5261

SQUAMOUS CELLS
EPITHELIUM SURROUNDING
±IMPLANT – FAILURE

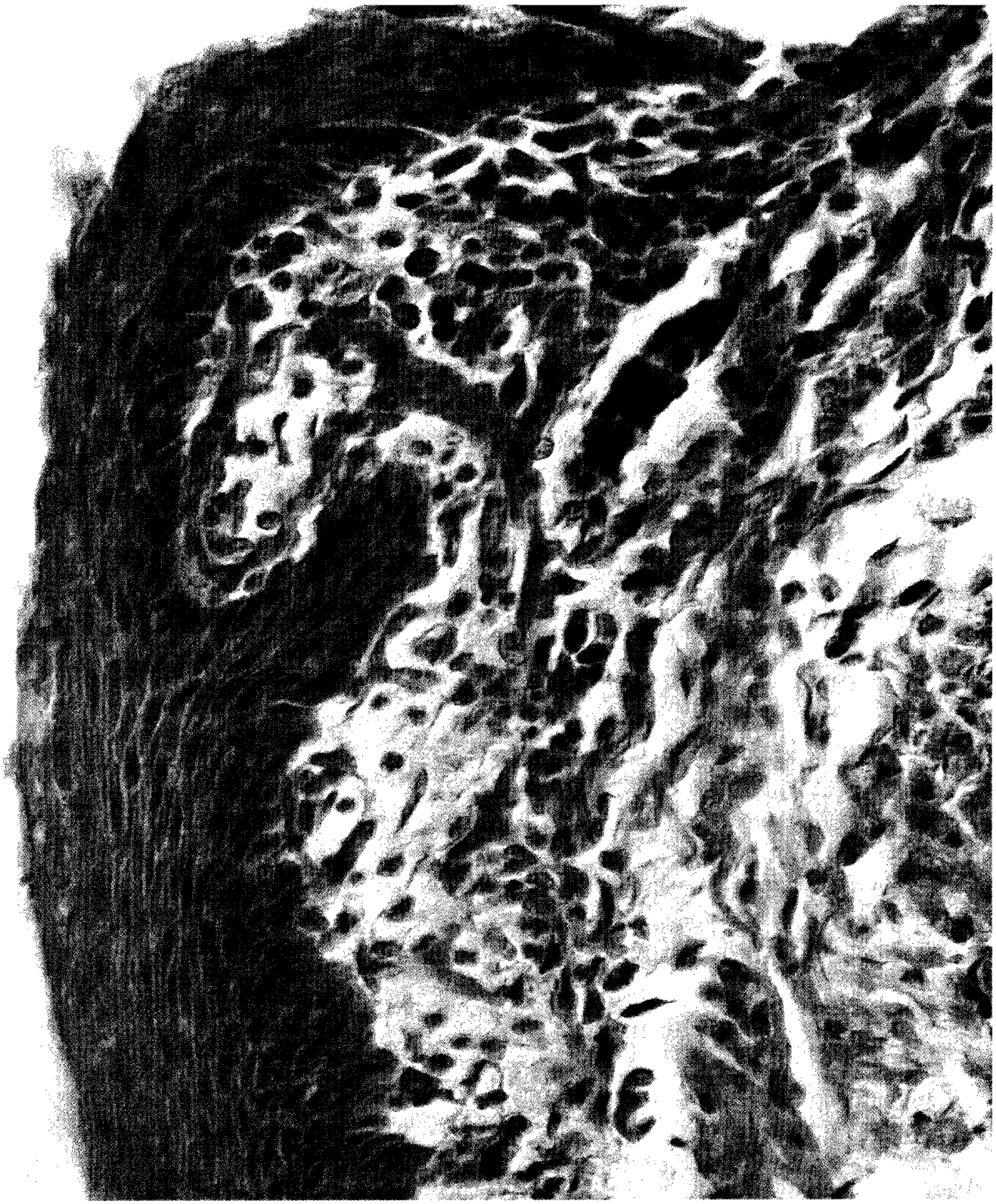
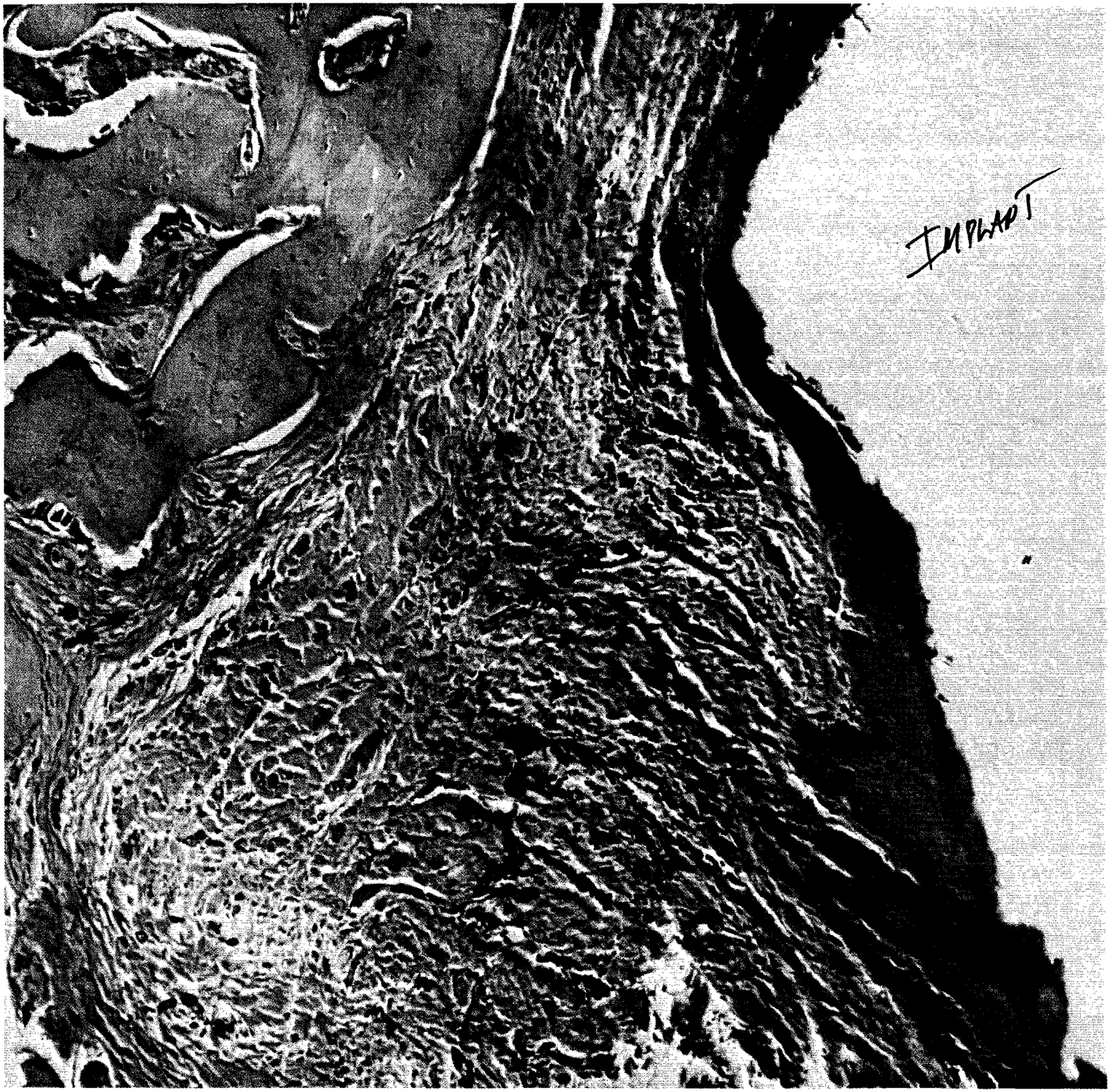


fig 3



#5261

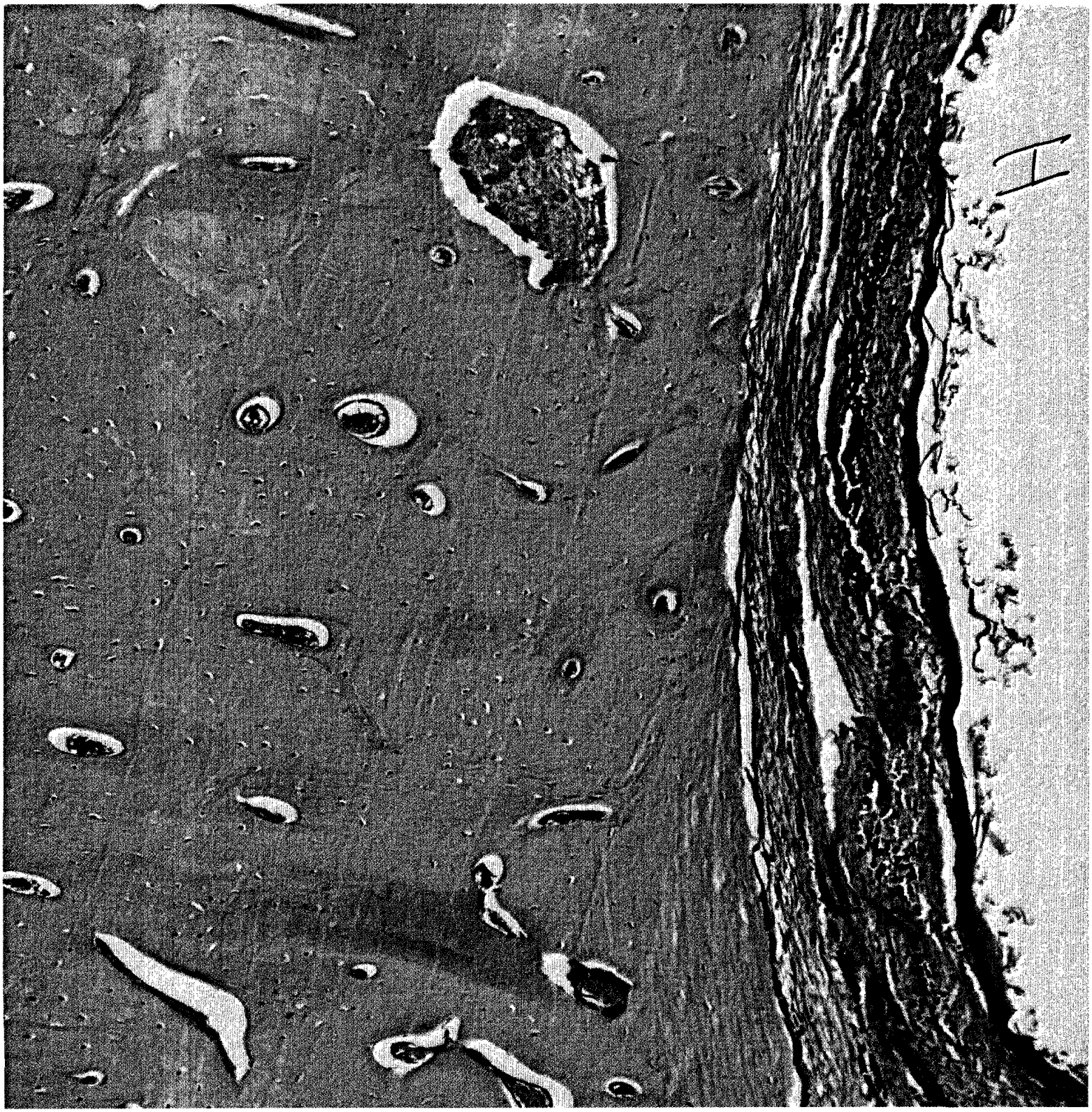
Squamous cell epithelium

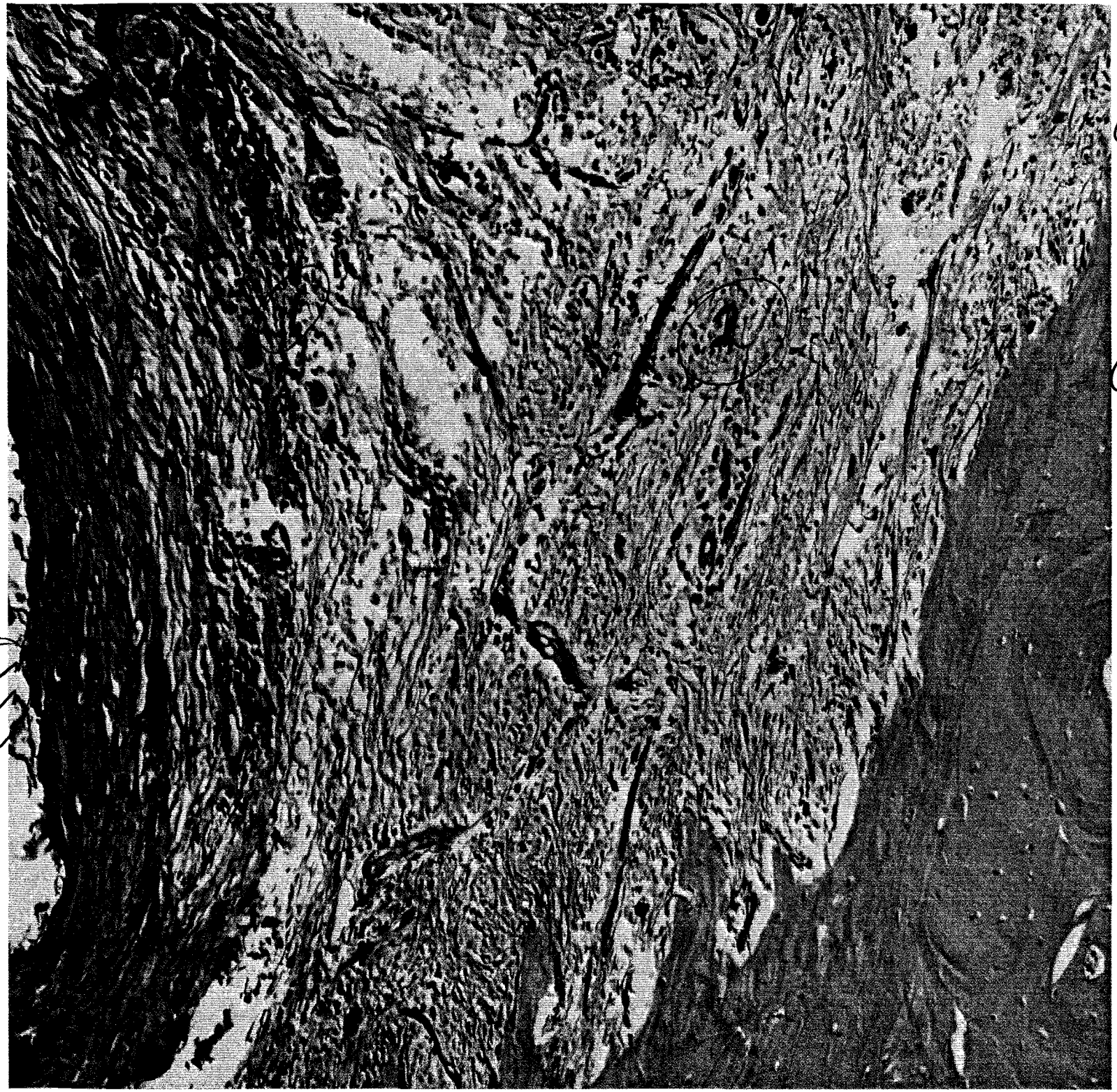
IMPLANT FAILURE

figure 4

EXHIBIT G

0577 fig 1
Chronic inflammation
around implant (FAILING)
C.T. membrane





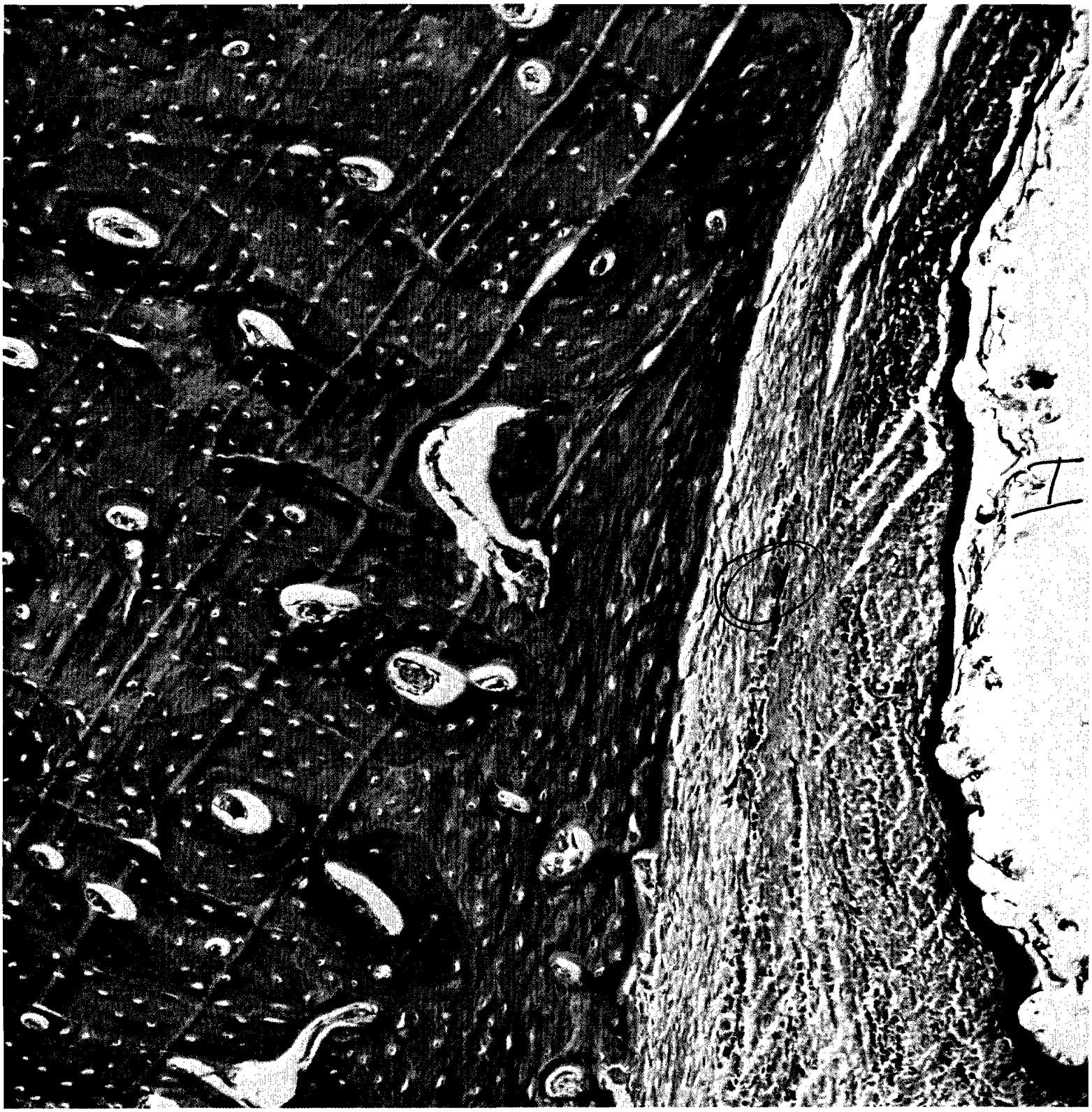
#0577
fig 2

(1) Chronic inflammation around failed implant

(2) Connective Tissue

0577 fig 3

(1) CONNECTIVE TISSUE LAYER
LOST IMPLANT



#0577
pg 4

(1) CONNECTIVE TISSUE SURROUNDING LOOSE PAILING IMPLANT

EXHIBIT H

1.

STUDY STOPPED
BECAUSE OF RABBIT PROBLEMS
WITH LH MATERIAL THAT TOOK
TOO LONG TO HARDEN

Title: Evaluation of Bioplant LC Handling and Effectiveness in Calvarium and Mandibular Defects in the Rabbit

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PROPOSED PROJECT PERIOD:

October 2002 - June 2003
August 2003 – March 2004
September 2003 – April 2004

Overview

Clinicians and researchers continue to search for the optimum bone replacement graft material (BRG) for use in periodontal, implant, and other oral surgical applications. A variety of materials and combinations have been used, but no one type of graft appears to be the best. With the increasing use of dental implants, it becomes even more important to find a BRG that will fill defects, bond to bone, stabilize the implant at the time of insertion, and improve esthetic contours.

Bioplant LC is a new light-hardened resorbable polymer material that can be engineered to provide the desired clinical and biological qualities necessary to achieve the above results. Its characteristics can be altered so that factors such as porosity, resorbability, hardness, etc., can be adjusted for the clinical problem being treated. Several different formulations with different characteristics of porosity, resorbability, etc. can be produced for different applications.

Hypothesis

We hypothesize that there will be significant differences in the handing characteristics, containment within bone defects, adherence to host bone, and the rate and amount of new bone formation with Bioplant LC formulations compared with Bioplant HTR (HTR).

Specific Aims

The purpose of this study is to evaluate Bioplant LC in four (4) different formulations (LC1, LC2, LC3, and LC4) regarding handling characteristics, containment within the defects, adherence to the host bone, and rate and amount of new bone formation compared to HTR alone and controls in the calvarium and mandible of rabbits.

Background

The animal model of calvarium defects and body of the mandible defects in rabbits has been used extensively to test host response to regenerative materials. Multiple operations can be performed inexpensively and with a relatively small amount of graft materials.

Bioplant HTR (Bioplant, Inc., Norwalk, CT) is a specific synthetic bone substitute that is a biocompatible microporous layered composite of PMMA (poly-methyl-methacrylate), PHEMA (poly-hydroxyl-ethyl-methacrylate), and a calcium hydroxide outer layer. HTR has shown effectiveness in treating periodontal defects and other oral bone loss problems [201,202,203,206,207,210,211,212,214,215,216,217,219,220,221,222]. The new Bioplant LC material has been described above. The LC form contains HTR as part of its complex.

The purpose of this study is to evaluate the handling, strength, biocompatibility, vascularization, bone formation, placement, adherence to bone, and healing following the grafting of four forms of LC and HTR alone compared to non-grafted controls in the calvarium and mandible of rabbits.

Research Methods and Protocols

Study Population

Fifty-six (56) female New Zealand white rabbits will be purchased and managed by the LSUHSC School of Dentistry Animal Care Committee for use in this study. The rabbits will be cared for under typical protocols to ensure that they remain healthy throughout the experimental time period. Forty-eight will be used for the project itself. The other eight will serve as backups if any animals die during the research.

Group Assignment

The surgical procedures on a given animal will be performed at the same single session to minimize morbidity.

The following scheme will be used to determine which side of the cranium and jaw receive LC1, LC2, LC3, LC4, HTR alone, or serves as an ungrafted control. Each of the five graft materials or non-grafted control will be used 8 times in 24 rabbits at each of the two time frames.

TABLE 1.

Assignments of Graft Materials and Healing Times Calvarium and Mandible			
Rabbit Numbers 4wks	**Rabbit Numbers 8 wks**	**Graft Material (Left)**	**Graft Material (Right)**
1	25	HTR	CTRL
2	26	HTR	CTRL
3	27	CTRL	HTR
4	28	CTRL	HTR
5	29	CTRL	LC3
6	30	LC4	LC3
7	31	LC1	HTR
8	32	LC1	LC2
9	33	HTR	LC2
10	34	LC2	LC4
11	35	LC4	LC3
12	36	LC2	HTR
13	37	HTR	LC2
14	38	LC3	LC1
15	39	LC1	LC4
16	40	LC2	CTRL
17	41	LC4	LC1
18	42	LC1	LC3
19	43	LC4	LC1
20	44	LC3	LC2
21	45	LC3	LC1
22	46	LC3	CTRL
23	47	CTRL	LC4
24	48	LC2	LC4

Sequence of Investigation

INITIAL PHASE

Purchase rabbits and acclimation

SURGICAL PHASE

Reflect flaps, create defects calvarium and mandible. Place LC1, LC2, LC3, LC4, HTR, or no graft (CTRL) in each segment according to code, close flaps and post operative treatment.

POT

Evaluate healing daily, then at 4 weeks or 8 weeks sacrifice and take block sections.

Sections will be assessed by histomorphometry using computer imaging. Data will then be analyzed according to area of bone healing across and within the defects.

Adherence to host bone of the LC1, LC2, LC3, and LC4 materials in the calvarium and mandible will be evaluated using an Instron instrument to measure the interfacial bone/graft strength of the graft/bone interface. Following the mechanical testing, SEM photomicrographs will be taken to evaluate the interdigitation of bone and LC materials.

Role of Investigators and Support Personnel

The surgical interventions will be performed by Dr. MaryAnn Brooks, Dr. Ioannis Vergoullis, Dr. Randy Malloy, Dr. Sotirios Vastardis, and Dr. Raymond Yukna. Histologic interpretation will be performed independently in a blinded manner on coded samples by Drs. Brooks, Vergoullis, Vastardis, and Yukna. Dr. Carr will serve as the histology advisor. Dr. Sarkar will supervise the mechanical testing. Statistical analysis will be performed with a commercially available computer statistical program (Prism). Dr. Mercante will be consulted for statistical assistance if necessary.

Methodology

Forty-eight large female New Zealand white rabbits, age 21-25 weeks, each weighing from 3.1 to 3.4 kg, will be used for this study (with eight additional animals kept as backups). General anesthesia will be induced in each animal with 40 mg/kg ketamine HCL, 1 mg/kg acepromazine and 3 mg/kg xylazine. Local anesthesia in the form of 2% Xylocaine with 1:100,000 epinephrine will be applied to the treatment areas before any of the surgical procedures. Assessment of satisfactory anesthesia will be based on non-reaction to pain from pinching toe tissues and lack of any eye reflexes.

Calvarium Defects –

A skin incision will be made in the midline of the top of the head. The subcutaneous tissue and muscles will be divided and reflected to expose the cranial periosteum, which will be incised laterally and elevated toward the midline. A 8mm trephine bur with water irrigation will be used to create two side by side circular defects lateral to the midline suture in the parietal bone. Care will be taken not to perforate the dura mater during drilling or on removal of the bone plug. By random allocation (Table 1), each calvarium defect will be grafted with an appropriate volume of either LC1, LC2, LC3, LC4, HTR alone, or left as an ungrafted control (with the same volume of GelFoam placed to maintain the space). This will provide 8 specimens with each treatment at each time frame. The periosteum and the skin flap will be replaced and sutured separately in layers with 5-0 or 4-0 gut or vicryl to obtain primary closure, and coated with triple antibiotic ointment and a cyanoacrylate bandage.

Mandibular defects –

The right and left side of the mandible will be incised at the inferior border and a full thickness flap will be reflected over the facial lateral aspects of the angle of the mandible. 5mm diameter through

and through defects will be created in the bone about 4mm coronal to the inferior border using a slow speed trephine bur with copious saline irrigation. Care will be taken not to traumatize the lingual musculature. Each defect will receive one of the graft materials or be a control as per the scheme in Table 1. The wounds will be sutured in layers with 5-0 or 4-0 Gut and/or Vicryl to obtain primary closure, and coated with triple antibiotic ointment and a cyanoacrylate bandage.

All rabbits will be administered oxytetracycline intramuscularly for bone labeling just after the surgery is finished (25 mg/kg body weight). By means of the bone labels, the newly formed bone should be distinguishable from residual bone during the histomorphometric analysis.

All animals will be checked daily for inappropriate healing or infection by the Animal Care Department or the primary investigator. Postoperatively, the animals will be maintained on a diet of water-softened Rabbit Chow pellets and water ad libitum. All rabbits will receive Buprenorphine (0.1mg) IM q12h for pain and 2,000,000 units of Bicillin IM for 4 days post-op. Three times per week, 0.2% chlorhexidine gluconate or Betadine will be topically applied to the surgical areas until the end of the experiment for each rabbit.

Histologic processing of specimens

The rabbits will be killed at the end of 4 or 8 weeks after grafting. Block tissue samples will be retrieved, coded, and transported in vials containing 10% zinc formalin to the LSUSD Research Histology Laboratory for routine processing (undecalcified sections cut in a lateral-medial plane of the calvarial defects and in an antero-posterior plane for the mandibular defects). One half will be embedded in Osteobed (Polysciences™), sectioned and ground to less than 20 microns in thickness using a Leitz Annular Saw Microtome for light microscope transillumination. Sections will be stained using toludine blue and alizarin red.

Mechanical Testing

Half of the calvarium and mandibular specimens will be evaluated for mechanical strength using interfacial bone/graft strength tests with the Instron testing instrument. That testing will be followed by SEM evaluation of the bone/graft interface.

Two pilot animals (receiving LC1, LC2, LC3, LC4) sacrificed at 4 weeks will be used to establish the technique for mechanical testing.

Interfacial bone/graft strength will be evaluated by trimming the blocks containing graft material so that acrylic block clamps can hold the bone adjacent to the graft site firmly and horizontally. A metal rod 7.5 mm in diameter will be moved against the superior aspect of the graft material with an Instron testing machine at a rate of 0.1mm/minute until the graft is pushed through the defect. The peak force measured divided by the interface area/circumference of the graft/defect will be calculated.

Following this mechanical testing, the bone interface surface will be evaluated by SEM after standard specimen processing.

The graft plug that was pushed through the defect will have its hardness determined using the Vickers Hardness Test, in which the specimen is mounted flat ground, and impacted with a diamond point.

Other samples will be light-hardened in disks in vitro mimicking the in vivo graft volume and shape and stored in physiologic tissue fluid. Compressive strength will be evaluated on 3 disks of each type at the equivalent of 4 and 8 weeks of implantation.

Histomorphometric analysis

Each image will be copied on color reversal film, digitized as a 256 x 256 array of 8-bit density values, and transferred to a microcomputer for analysis of bone volume fraction (which is percent new bone, percent old bone, and size of defect) in the augmented area. In addition, rate of resorption (related to freshly grafted specimens) and revascularization will be evaluated. (See Figure 2). The Bioquant Image Analyzer and the NIH IMAGE image analysis program (National Institutes of Health, Bethesda, MD) will be used for the analysis.

Errors of the Histometric Methods.

The variability in measuring the histometric parameters will be assessed by analyzing the difference between duplicate measurements made 1 week apart from five different sections, and method errors will be calculated[15]. The sections will be coded and evaluated blindly in random order.

Statistical analysis

Due to the sample size (8 with each application at each time frame) the report of the findings will be primarily descriptive. Means $\pm$ standard deviations will be calculated for the different histometric measurements. A table of the results will be made to present the findings for comparison. After the descriptive data is reviewed, a statistical analysis will be performed to determine any significant differences. One way ANOVA with Duncan Multiple Range post-test will be used to compare differences in the various parameters measured. These comparisons will determine if there are differences among the treatments. An alpha of $p < 0.05$ will be used to determine statistical significance. The Mann Whitney U test may be used for each pair of treatments.

Potential Difficulties

In the case that any of the animals becomes ill or dies, rabbits from the replacement pool will be used, but even then the small sample size could compromise the validity of the results. Randomization of time frames has been used to minimize the problem. Animals may also interfere with the healing of the wound over the materials, but good tissue closure and proper suturing should minimize that concern.

Data Collection Procedures

Block sections will be collected at 4 weeks and 8 weeks and processed for histologic evaluation. Two investigators will independently, blindly and randomly evaluate each histologic slide. The scores will be compared and a percentage of agreement calculated. If the two investigators are discrepant, they will review the slide to come to a consensus on the rating. Radiographs of the block sections prior to histologic processing will be randomly analyzed by Bioquant Image Analyzer for determination of the amount of radiographic density.

Evaluation

Two raters will individually, blindly, and randomly evaluate each histologic section. The rater scores will be compared and a percentage of agreement calculated. If the two raters are discrepant by more than one grade, they will review the section to come to a consensus on the rating. The agreed upon values will be used for the statistical analysis.

Data Forms

See Addenda.

EXHIBIT I

2.

Evaluation of Bioplant Light Cured Bone Graft Replacement Materials

A Thesis

Submitted to the Graduate Faculty of the Health Sciences Center of

Louisiana State University and

Agricultural and Mechanical College

in partial fulfillment of the

requirements for the degree of

Master of Science

In

Oral Biology

By

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B.S., University of the Incarnate Word, 1997

D.D.S., Baylor College of Dentistry- TAMUHSC, 2002

Certificate in Periodontics, Louisiana State University, 2005

June, 2005

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Abstract

Evaluation of Bioplant Light Cured Bone Graft Replacement Materials

Background: Bone Replacement Grafts (BRG) are often used to improve healing in large bony defects. Following surgery, the stability of many bone graft materials becomes questionable, thus reducing their effectiveness aiding in boney repair.

Purpose: The purpose of this study was to evaluate Bioplant LC(a light cured BRG) regarding the amount of new bone formation compared to commercially available HTR BRG alone (positive control) and ungrafted (negative control) in the skull defects of rabbits at 4 and 8 weeks, as well as the tissue response during the healing period. The effect of Bioplant LC on UMR cell survival was also evaluated..

OLD MAT PART I

Material/Methods: An 8mm circular defect was created in the skulls of rabbits using a trephine bur. Light Curable graft materials were placed in the defects, and cured using a Optilux 400 Light curing source for 4 min. Tissue response was evaluated daily, then at 4 or 8 weeks the animals were sacrificed and the defects retrieved for histological examination. Light Curable graft materials were also evaluated for toxicity in vitro, using UMR-106 osteosarcoma cells.

Results: Most animals with the LC test material implanted exhibited morbidity or mortality at or prior to the 4 or 8 week end point and were sacrificed. Gross tissue healing showed swelling and necrosis in most test animals, and none of either of the controls. Histological evaluation in all test animals showed inflammatory cells, necrotic bone particles with few new bone particles, plasma cells, and giant cell reactions. In vitro, LC materials induced death in cultured cells in as little as 2 hours. By 6 hours, cell death had spread laterally and by the 48 hour mark cell death was widespread. The extent of and rate of death was different for the different Light Cured materials examined.

Conclusions: The Bioplant Light Curable bone replacement graft materials studied caused significant cell death in-vivo and in-vitro.

Introduction

I. Bone Replacement Grafts

When bone is lost intra-orally from disease, injury, or congenital defect; a clinician must choose how to rebuild the defect area. One of the many options available to clinicians, is bone replacement graft (BRG) materials. The use of tissue compartment separating materials such as BRG's is based on the biologic principles of guided bone regeneration (GBR). This concept is based upon the assumption that only the bone cells have the potential for regeneration of missing alveolar bone. Barrier or space occupying materials are used to separate tissue compartments during healing so that the desired tissues/cells (periodontal ligament, alveolar bone, or both) occupy the wound space first. Excluding the epithelium and gingival connective tissue from the area during the postsurgical healing phase favors repopulation of the area by bone cells. This has been histologically shown to occur to some degree in animals and in humans[i].

Clinical results with BRG's have been quite favorable. The type of material used may not be as important as having some space maintaining material in place at all. It is important that the material stay in place in a stable manner for the required time. During GBR, the single most important concept is space maintenance beneath the membrane[ii,iii]. It appears that a combination of BRG and membrane will maintain space most effectively and enhance bone regeneration. It is also suggested that use of a material or substance that may stabilize the wound and protect the root surface-adhering fibrin clot from tensile forces acting on the wound margin is important[iv]. Particulate BRG's need this protective membrane covering to contain the graft and prevent non-bone cell types from infiltrating among the BRG particles. A light-curable, solid forming BRG may preclude the need for

a membrane. Bone replacement graft materials come from numerous sources including human, animal, and synthetic.

a. Autografts

A widely used intra-oral BRG comes from the same patient or animal. Ellegard and Loe studied and suggests that osteoconduction effects represent the essential mechanism by which mature autogenous cancellous bone transplants promote bone formation.[v] In studies in patients, full regeneration of the bone within the periodontal defect with autogenous use was found to be 72% in 3-wall, 45% in 2-wall, and 40% in combined. 80% of 3-wall or 70% of 2-wall healed to more than half of original defect. [vi] Although, autografts have shown to be a successful BRG, some patients and indications do not allow for their use. As one alternative, an alloplastic or synthetic material can be used.

b. Alloplasts

Synthetic bone replacement graft materialshas been reported in the periodontal literature with good clinical results. Pourous hydroxylapatite BRG (P-HA) has been used in the form of block grafts has been shown to have the potential to enhance development of osseous tissue within its' pore structure and is also slowly broken down by the tissues within it[vii]. Other researchers showed with their studies that other synthetic BRGs in particulate form can give better results in treating periodontal defects versus open flap debridement alone[viii, ix, x, xi]. All of the above studies evaluated the results of the treatments studied with either re-entry or clinical measurements. Additionally, there are a large number of animal and human studies that prove the ability of synthetic BRGs to enhance new bone formation at the histologic level[xii, xiii, xiv]. One type of synthetic material is HTR (Hard Tissue Replacement).

i. HTR

Bioplant HTR (Bioplant, Inc., Norwalk, CT) is a specific synthetic bone substitute that is a biocompatible microporous layered composite of PMMA (poly-methyl-methacrylate), PHEMA (poly-hydroxyl-ethyl-methacrylate), and calcium hydroxide. HTR has shown effectiveness in treating periodontal defects and other oral bone loss problems[xv xvi xvii xviii, xix, xx, xxi, xxii, xxiii, xxiv, xxv, xxvi, xxvii, xxviii, xxix, xxx]. Yukna (1990) used HTR for treatment of 1, 2 and 3 wall intrabony defects in 27 patients and found that the HTR grafts resulted in significantly better defect fill of 2.2mm (60.8%) compared to 1.0mm (32.2%) for the controls (Open Flap Debridement alone). 71% of the defects had more than 50% bone fill response to HTR compared to 24% for the controls. These results achieved with HTR are equivalent to the results reported with other bone graft materials used in literature.

ii. Light Cured BRG (LC)

Current particulate BRG's can be difficult to deliver to the surgical site; do not readily stay where placed; and can be deformed, displaced, or lost due to flap manipulation. This is mainly due to lack of adhesion of particulate material to itself, tooth, and bone. Particulate forms do not form a firm cohesive, stable mass. The Bioplant LC BRG is a synthetic material in a form that may contain HTR as part of its complex. The advantage of the LC material is that it may address the drawbacks to particulate BRG's because it can be hardened by light curing. This hardening would allow a cohesive, stable bone graft formed in the defect area with chemical and mechanical bonding to the adjacent host bone. Four formulations of this new Light Cured BRG materials were used with differences in composition and resorption intervals.

II. Purpose

The primary purpose of this study was to evaluate the amount and rate of new bone formation following LC application in the bone defects in the skulls of rabbits.

III. Hypothesis

The hypothesis of this project was:

1) Bioplant LC formulations will result in higher amount of new bone formation compared to HTR alone and un grafted controls in the skulls of rabbits.
2) Bioplant LC will have faster rate of new bone formation compared to HTR alone and ungrafted controls in the skulls of rabbits.

If this hypothesis proved to be true, it would provide a new option for regenerating bone and facilitating the maintenance or replacement of teeth. This was the first in vivo study to examine the Bioplant LC or any Light Cured BRG currently available in vivo. If the results were positive, the next step would be to experiment with the material in periodontal and peri-implant type defects in skulls of higher animal forms and eventually in human clinical trials.

IV. Rabbit Model

Background on Model

A number of innovations have been made to optimize bone repair, but before their use in humans, extensive animal trials must be performed to establish efficacy and safety. The rabbit calvarium model has been used extensively in the past[xxxi] and was therefore the animal model chosen for this study of these new bone graft materials.

a. Materials and Methods

Forty-eight (48) female New Zealand white rabbits were purchased and managed by the LSUHSC School of Dentistry Animal Care Committee for use in this study. At day 0, 24

of the rabbits were purchased and 4 weeks later 24 more weree purchased in order to reduce the cost of maintenance of the rabbits and to overcome any problems of space limitations for keeping the rabbits in the LSUHSC School of Dentistry Animal Care Department. The rabbits will be cared for under typical protocols to ensure that they remained healthy throughout the experimental time period. Four more rabbits were purchased and served as backups in case that any of the animals participating in the study died during the study.

On the day of surgery, local anesthesia was administered to the top of the skull (1 carpule lidocaine 1:100k epinephrine in total, for both sides). Full thickness flaps were reflected and an 9mm circumferential inner and outer bone cortex defect was created with a 9mm total diameter, with 8mm internal diameter, trephine bur on the skull lateral to the midline suture (Refer to picture 1). Coded materials were placed into each defect: either LC-1, LC-2, LC-3, LC-4, HTR, or no material (see code assignment Table 1 and 2). The following scheme (see Table 3) was used to determine which side of the skull received LC, HTR alone, or served as an ungrafted control. This scheme was used to insure even distribution of the treatments. The Bioplant LC graft materials were used 64 times while the HTR graft material and the non-grafted control was used 16 times in the 48 rabbits at two different time intervals, 4 and 8 weeks. For the 4 week healing interval: 32 defects received one of the Bioplant LC materials, 8 defects received the positive control material (HTR) and 8 more received the negative control treatment (ungrafted). In the second group of rabbits, another 48 defects were treated, with one of the Bioplant LC materials placed into 32 defects, HTR (positive control) placed into 8 defects and 8 more defects left ungrafted (negative control). 64 defects in total received the LC test material with 16 each receiving LC-1, LC-2, LC-3, LC-4, 16 HTR and 16 no graft. Several studies have examined the HTR and no grafting treatment modalities and served as references to support and make valid the information that the specimens from this study

too long

provided. Sites receiving an LC graft were light cured with an Optilux 400 Light curing source for 5 min, then the soft tissues were sutured with gut internally and vicryl externally in two layers. Iodine solution, an antibiotic ointment and spray bandage was applied after suturing was completed. All rabbits will be administered oxytetracycline intramuscularly for bone labeling just after the surgery was finished (25 mg/kg body weight). However this method of analysis was not used due to technical reasons.

Animals were monitored daily. If inappropriate healing or infection occurred, a staff veterinarian was consulted for appropriate medication and/or treatment needed (antibiotics, intravenous fluids, heat, sacrifice, etc). Postoperatively, the animals were maintained on a diet of water-softened Rabbit Chow pellets and water ad libitum. All rabbits received Buprenorphine (0.1mg) IM q12h for pain and 2,000,000 units of Bicillin IM for 4 days post-op for infection control. Three times per week, 0.2% chlorhexidine gluconate or Betadine was topically applied to the surgical areas until the end of the experiment for each rabbit.

At 4 or 8 weeks according to group assignment[xxxii], animals were sacrificed and block sections were taken and transported in vials containing 10% zinc formalin to the LSUSD Research Histology Laboratory for routine processing (decalcified sections cut in a lateral-medial plane of the calvarium defects). The sections were stained with Hemotoxylin and Eosin and the most central sections to the area of the defect were analyzed.

b. Results

A significant number of animals that received Light Curable material exhibited morbidity or mortality at or prior to the 4 or 8 week end point and were sacrificed in compliance

with animal care guidelines. Because of the rapid development of negative healing responses in animals which received the LC test materials, only 24 of the planned of 48 rabbits were operated on. Several rabbits were then operated on to rule out surgical technique, effect of the curing light on hard and soft tissue, the effect of material touching the dura mater of the brain (by placing a membrane prior to placement of the test materials), and surgical site (calvarium vs tibia). All of the rabbits healed uneventfully without LC in place and the histology resembled our ungrafted (negative) control.

Gross tissue healing was normal in both control groups (see picture 2).

Most test animals showed swelling and soft necrosis (see pictures 3,4).

Histological evaluation of positive control sites (HTR) showed few inflammatory cells, presence of HTR particles, connective tissue, and sparse new bone formation (see pictures 5,6). The negative control sites (ungrafted) showed no inflammatory cells, connective tissue, and new bone (see picture 7,8). The various LC test sites showed inflammatory cells, necrotic bone with very few new bone particles, plasma cells, and giant cell reactions around the LC test material (see pictures 9-12). Defect fill was not analyzed due to the inability to complete the full time period for analysis.

Due to the gross and histological events seen with the LC materials, further examination of the effects of these materials was indicated. An in-vitro study was established and performed to determine of the LC materials at the cellular level.

V. In-Vitro Model

Background

Due to the problems that occurred in the animal model with the test materials, an in-vitro model was established. The live/dead cell viability/toxicity assay was chosen due to its extensive use in the literature and the simplicity of the assay.[xxxiii]

a. Materials and Methods

Four different LC test materials, one positive control (HTR) and a negative control (no graft) for a total of 6 variables were used in this study. Light cured discs of the LC materials, 2mm in circumference, were prepared in advance. These materials were bench light cured as per manufacturers recommendations for 5 minutes per sample.

1. Cell preparation - Rat osteosarcoma cells (UMR106 – ATCC # CRL-1661)

Rat Osteosarcoma Cells (Osteoblasts) were obtained from the American Type Culture Collection. These osteoblasts are a line of fetal osteoblasts (obtained from a spontaneous miscarriage) that have been transfected with a temperature sensitive expression vector (pUCCSVtsA58) and with a neomycin resistance expression vector (pSV2-neo) and were grown at 33°C to prevent their temperature sensitive auto-differentiation. They are a defined cell population that act as references for transcript expression by Periodontal Ligament cells and gingival fibroblast isolates. These cells were maintained in DMEM/F12 without phenol red, 10% fetal bovine serum (FBS) and 200 IU/ml of penicillin and 200 μg/ml streptomycin at 37°C and no gases as per manufacturer's instructions.[xxxiv]

2. Experimental assay to measure the induced cell death proximal to material microscopically:

6-well plates, 4 plates with 4 repeats for each material (see table 4) were used for this in-vitro study. Specifically, UMR-106 cells[xxxv] were added into each well (containing media with serum) of a 6-well plate, and allowed to adhere for 18 hours. Roughly $5x10^4$ cells were added to each well, in order to produce an evenly distributed layer of cells, that covered approximately 25% of the total surface area of the well.

Prior to adding the various BRG materials to the plates of UMR-106 cells, Ethidium Homodimer and Calcein were added to the cells (part of the Live/Dead Viability/Cytotoxicity Kit: L-3224)[xxxvi]. Live cells were distinguished by the presences of esterase activity, determined by the enzymatic conversion of the non-fluorescent Calcein to an intensely fluorescent green Calcein. The Calcein had a absorption/emission of 494/517 nm. Ethidium Homodimer entered the damaged membranes of affected cells and was bound to the nucleic acids in the nucleus. This stain emitted a red fluorescence at an absorption/emission of 528/617. Ethidium Homodimer was excluded by the intact plasma membrane of live cells. The UMR-106 cells were allowed to grow normally at 37°C for up to 48 hours after the materials were added to the plates. At 0, 2, 4, 6, 12, 24, and 48 hours, the materials were removed from the plates and a flat bed laser scanner (Typhoon 9400) was used to produce an image based on the wavelengths of the different dyes (see picture 13). [xxxvii]

The Typhoon 9400 is a highly sensitive variable-mode gel imager. This scanner allows the ability to detect an extensive variety of fluors with proven storage phosphor autoradiography technology and direct imaging of chemiluminescence. Powerful excitation sources and high quality confocal optics allow for sensitive detection of low expression targets. This imager delivers outstanding linearity, quantitative accuracy and extremely low limits of detection. The Typhoon also allows automated multicolor scanning and permits detection of multiple samples in the same experiment (see table 5 for emission and filters).[xxxviii]

b. Results

All four formulations of the Light Cured BRG material induced death in UMR-106 cultured cells. In as little as 2 hours (for those cells in direct contact with the materials) cell death had begun for all the LC materials. By 6 hours, cell death had spread laterally from the material for LC-2 and LC-4. By the 48 hour mark cell death was widespread, encompassing the entire test well for LC-2 and LC-4 (the materials that also contain HTR). At 48 hours, LC-1 and LC-3 cell death had progressed laterally from the material. The extent of and rate of death was different for the different Light Cured materials examined. Both control materials (HTR and no graft material) stayed consistent with little cell death. (see pictures 14-20).

Statistics agreed with the gross observations (see tables 6-8).

VI. Discussion

The idea of a Light Cured bone replacement graft material has validity. It could solve many of the problems that arise with commonly used particulate materials. LC could provide

primary clot stability of the material which is crucial for proper bone formation. It also could make improve the handling characteristics due to it's ease of use.

The adverse healing in our animal model did not allow for the planned histologic analysis of the various LC BRG's. Thus, no comparison to other animal studies with BRG's could be accomplished. Comparison of the HTR (positive control) and ungrafted control (negative control) showed similar results histologically and cellularly to previously reported literature.[xxxix]

The method of the toxicity is not evident at this point. To determine the mechanism of cell death, an apoptosis assay could be used to rule out programmed cell death. Several hypotheses of the cause of the toxicity have been suggested. One of the most obvious suggestions is that the material never fully cured in vivo. Two possiblilities for why it did not fully cure are that blood/fluid during surgery and/or storage of the material at a specific temperature/humidity/time interval inactivated the full setting potential of the materials. The blood/fluid hypothesis was proven incorrect by the in vitro study since the LC materials were bench cured prior to placement with the cells. Two of the formulations of the LC (LC-2, LC-4) material were more toxic. These two materials have HTR particles added to the light cure material. One proposed reason for the increased toxicity of these two formulations is that the porosity of the HTR may harbor material that never cures and could leach out into the adjacent tissue, causing cell death.

As for the in-vitro model system used, this is the first reported used of the toxicity assay analyzed with the Typhoon machine, and may prove to be a reliable method for in-vitro testing of material in the future. This model system allows for a much more accurate reading of the cell layers within the wells. In the past, a plate reader would read the entire volume of

the well in order to obtain the desired count of live/dead cells. Typhoon, reads the specific layer where the cells are located in the media. This eliminated false readings of the media in the wells and focuses just on the cellular layer in the wells.

VII. Limitations of the study

The main limitation in this study was the unexpected adverse effects of the LC test materials in the animal model. The tissue necrosis, inflammation, animal morbitity and mortality, and inability to finish the study time interval in the test samples seriously affected the histologic evaluation. This in turn affected the ability to measure the amount of new bone formation, percent defect fill, or bond strength to the host bone. When problems arose, care was taken to rule out surgical technique as well as surgical site. Animals that received only control treatments had no adverse effects. This showed that the technique was safe for our study. We treated several extra rabbits with a membrane placed down prior to the LC material being placed. These rabbits also showed soft and hard tissue adverse effects due to the LC materials. The light source was also ruled out as a potential negative effector by applying the light source for the 5 minutes the several rabbits with ungrafted defects. These rabbits as well showed no negative adverse healing patterns. At this point, the assumption was made that the toxicity was due to the material itself.

In the in-vitro model used, direct cell death was measured. One of the big drawbacks to cell death conclusions, is the inability with the assay to determine the route of cell death (apoptosis vs necrosis). Due to the advanced and encompassing nature of toxicity by the LC test materials, the method of cell death is probably irrelevant. Observation under the microscope of each well was performed, prior to scanning at each time point, to validate the effect of the various BRG materials on the cells. The observations were parallel to

immunofluoresence. The in vitro sample size was small with 4 repeats for each material, but this was used as an adjunct to verify the animal results.

VIII. Conclusions

Four formulations of such a material were tested in animal and in-vitro models. At this time, all four formulations of the Bioplant LC materials are toxic in-vivo and in-vitro.

Much more testing of these particular light cured bone replacement materials is warranted prior to further animal or human testing.

TABLE 1. Code Assignment-4 Weeks

Assignments of Graft Materials and Healing Times (4 weeks)		
Rabbit Numbers	**Graft Material (Left)**	**Graft Material (Right)**
1	HTR	LC
2	LC	CTRL
3	HTR	LC
4	HTR	CTRL
5	CTRL	LC
6	LC	LC
7	LC	HTR
8	LC	LC
9	HTR	LC
10	LC	LC
11	LC	LC
12	LC	HTR
13	CTRL	HTR
14	LC	LC
15	CTRL	HTR
16	LC	CTRL
17	LC	LC
18	LC	LC
19	LC	LC
20	LC	LC
21	LC	LC
22	LC	CTRL
23	CTRL	LC
24	LC	LC

TABLE 2. Code Assignments-8 Weeks

Assignments of Graft Materials and Healing Times (8 weeks)		
Rabbit Numbers	**Graft Material (Left)**	**Graft Material (Right)**
25	HTR	LC
26	LC	CTRL
27	HTR	LC
28	HTR	CTRL
29	CTRL	LC
30	LC	LC
31	LC	HTR
32	LC	LC
33	HTR	LC
34	LC	LC
35	LC	LC
36	LC	HTR
37	CTRL	HTR
38	LC	LC
39	CTRL	HTR
40	LC	CTRL
41	LC	LC
42	LC	LC
43	LC	LC
44	LC	LC
45	LC	LC
46	LC	CTRL
47	CTRL	LC
48	LC	LC

Table 3. Experimental design

Day 0 (WEEK 0)

24 rabbits

48 defects

8 defects	8 defects	8 defects	8 defects	8 defects	8 defects
HTR	Cntrl	LC-1	LC-2	LC-3	LC-4

WEEK 4

24 new rabbits

48 defects

8 defects	8 defects	8 defects	8 defects	8 defects	8 defects
HTR	Cntrl	LC-1	LC-2	LC-3	LC-4

WEEK 8 (from Week 0)

Sacrifice all the animals

TABLE 4. In Vitro Material Well Assignment

LC – 1	LC- 2	LC- 3
LC - 4	HTR	No Graft Material

Table 5. Typhoon 9400 Laser Light Source and Emission Filters

Color	Wavelength	Light Source
Red Light	632.8 nm	Helium - Neon Laser
Green Light	532 nm	Solid State doubled frequency SYAG laser
Blue Light	488 nm	Argon Ion Laser
Blue Light	457 nm	Argon Ion Laser

Emission Filters	
520 nm band pass	Cy2, ECL Plus, Fluorescein
555 nm band pass	R6G, HEX
580 nm band pass	Cy3, Tamra
610 nm band pass	Sypro™ Ruby, ethidium bromide
670 nm band pass	Cy5
526 nm short pass	Fluorescein
560 nm long pass	TRITC

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3.

Table. 6 Graph of Percent Live Cells

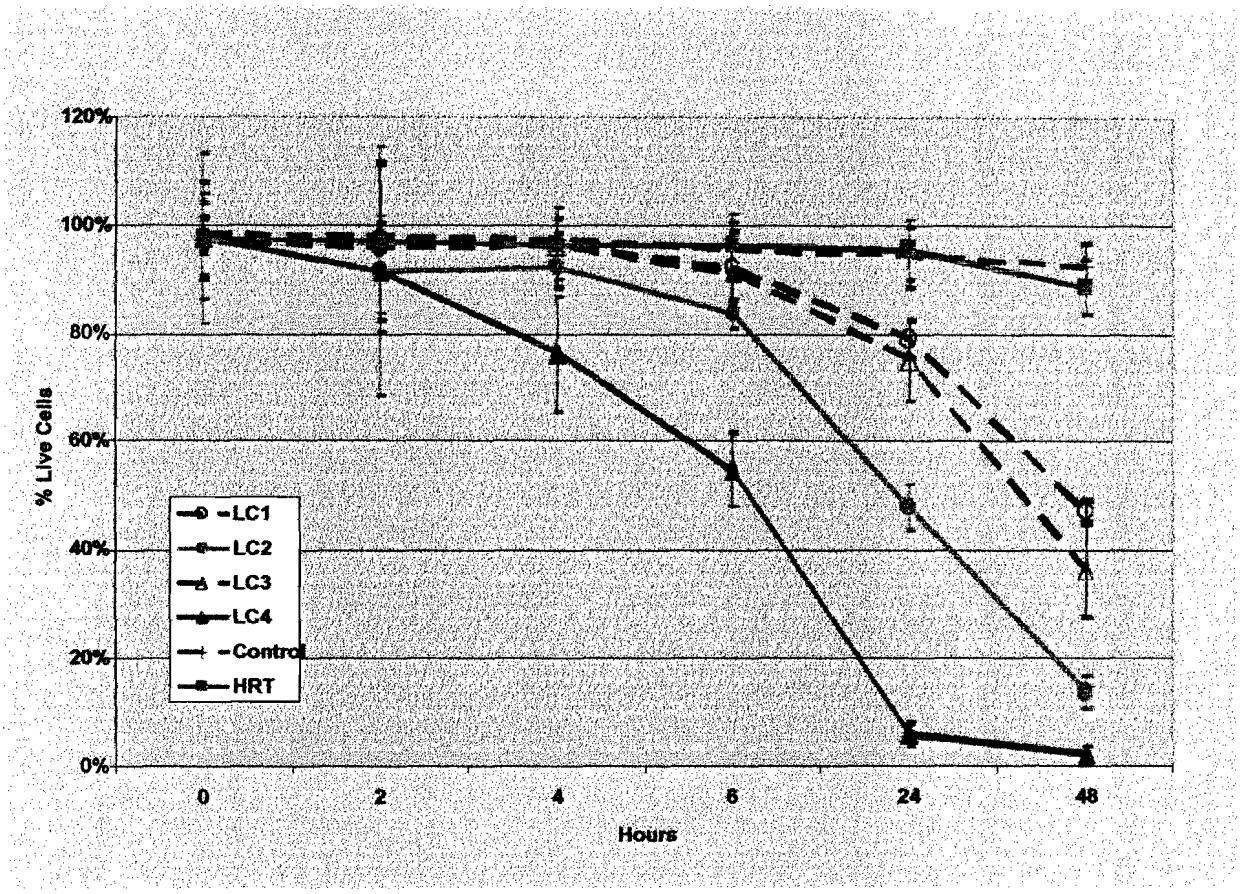
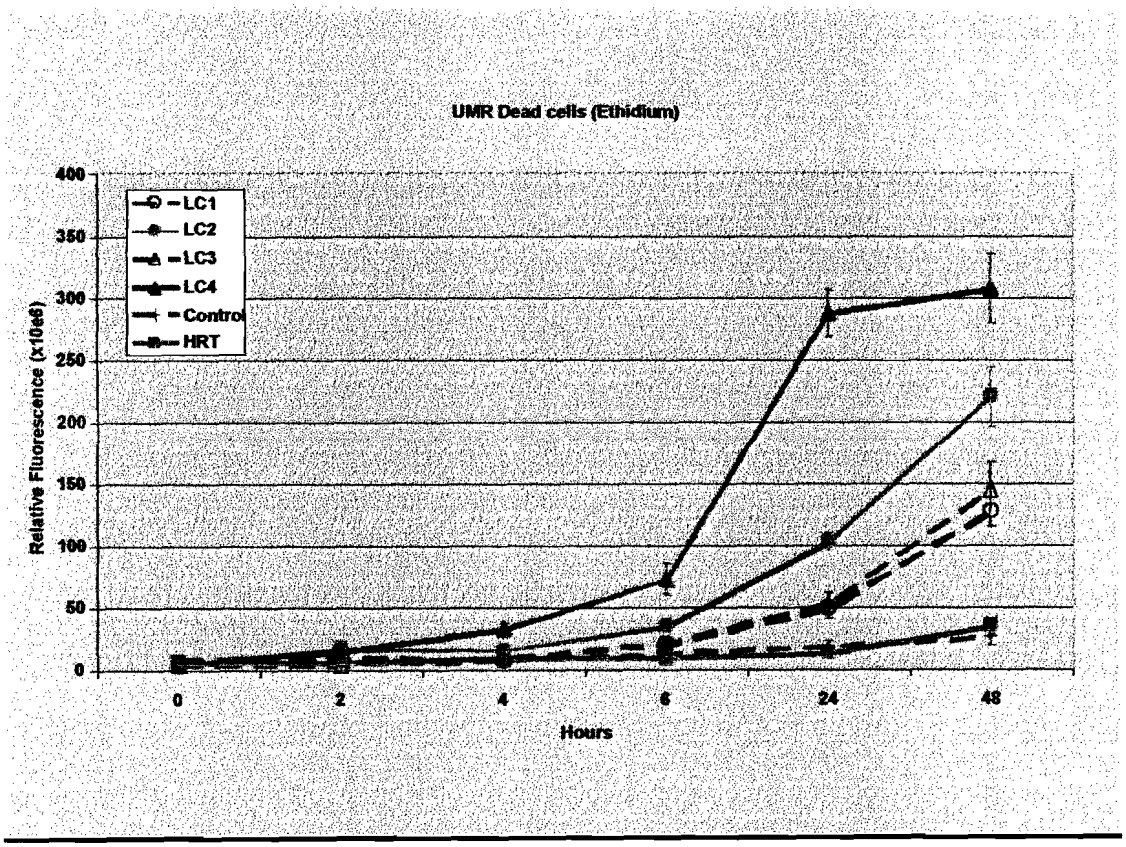
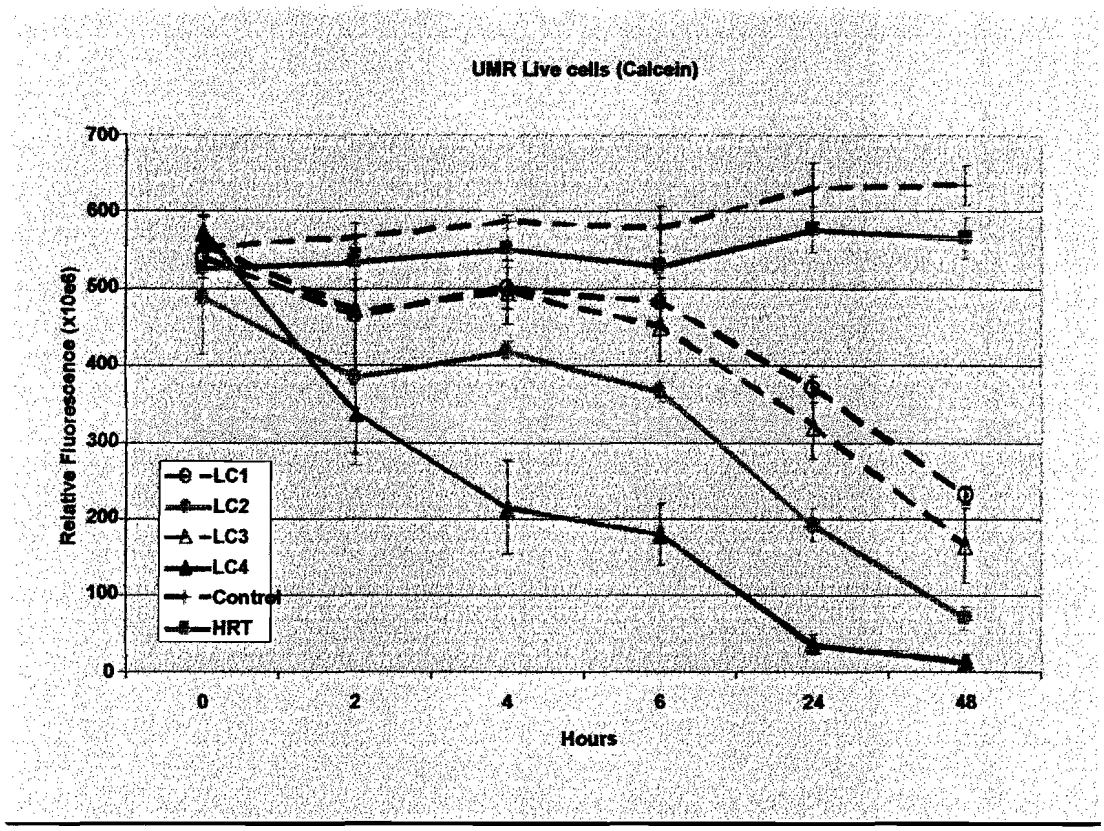


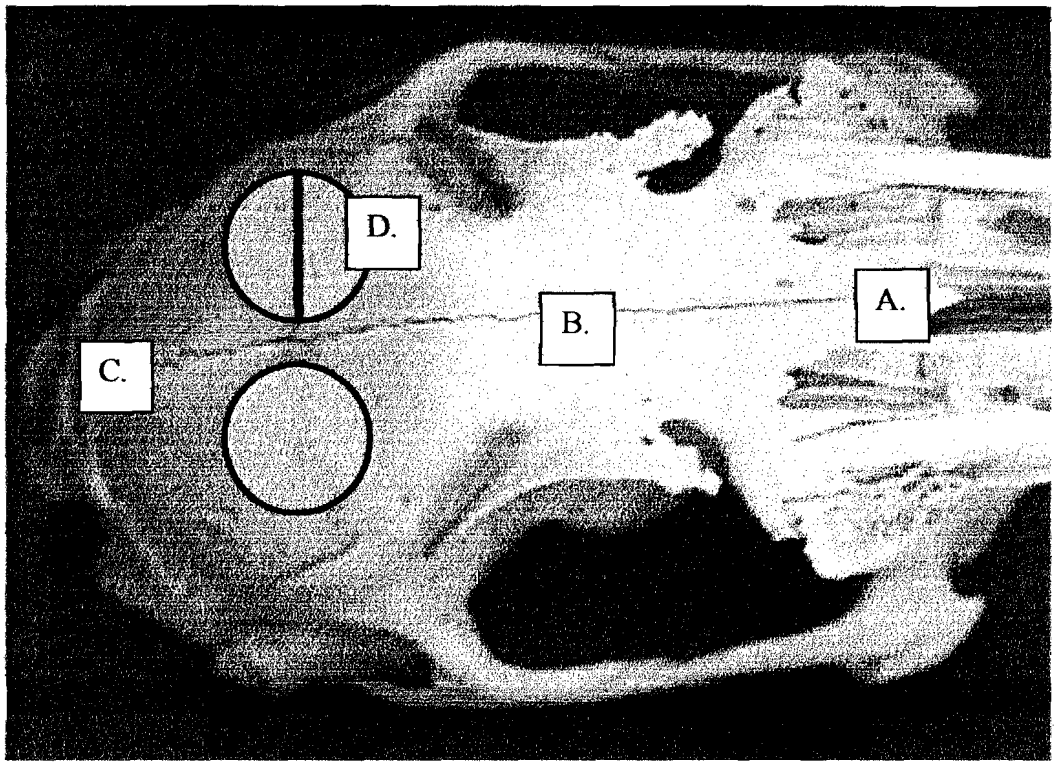
Table 7. Graph of Relative Fluorescence-Ethidium Bromide (Dead Cells)



Graph 8. Relative Fluorescence-Calcein (Live Cells)



Picture 1. Skull Defects



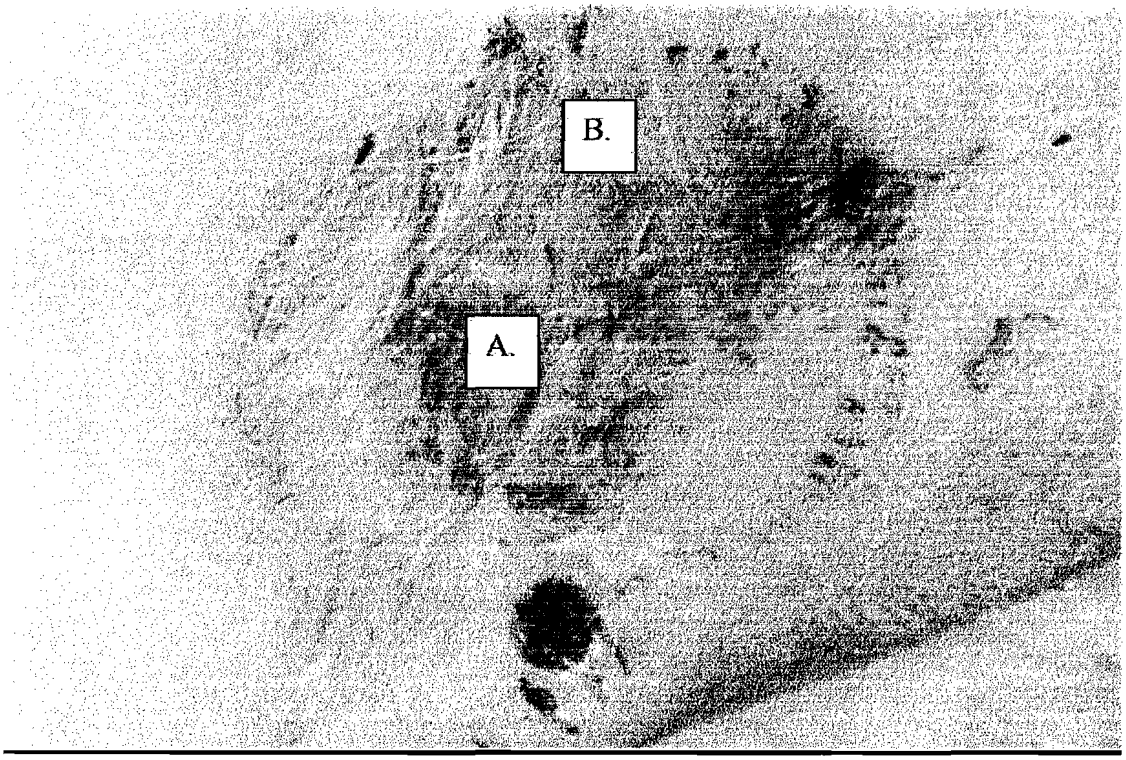
A. Anterior area of skull

B. Midline suture

C. Posterior area of skull

D. 8mm circumferential defect lateral to the midline suture

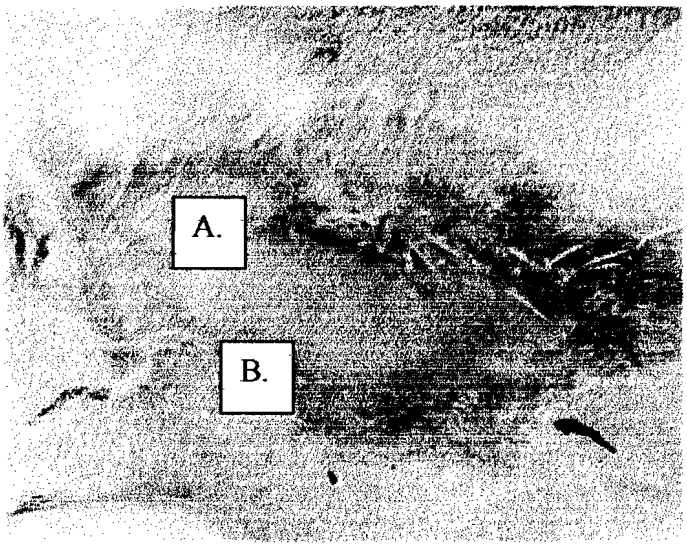
Picture 2. Normal Soft Tissue Healing – Control Animals



A. Suture line completely closed

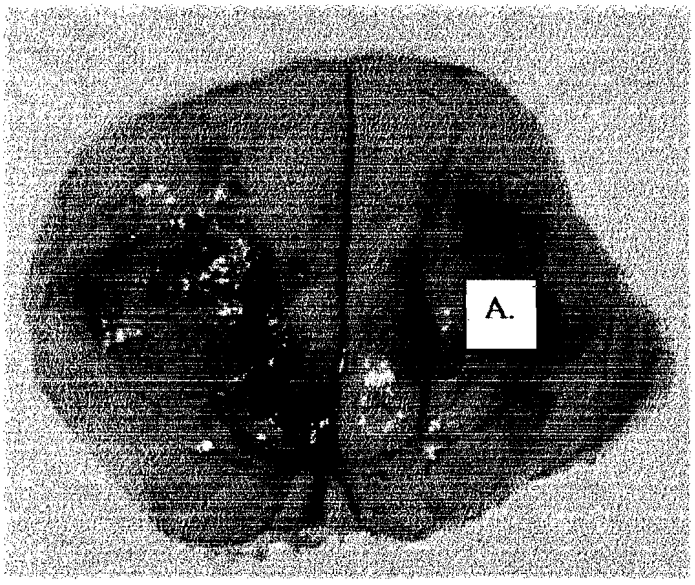
B. Little inflammation of area – light pink in color

Picture 3. Adverse Soft Tissue Healing – LC site



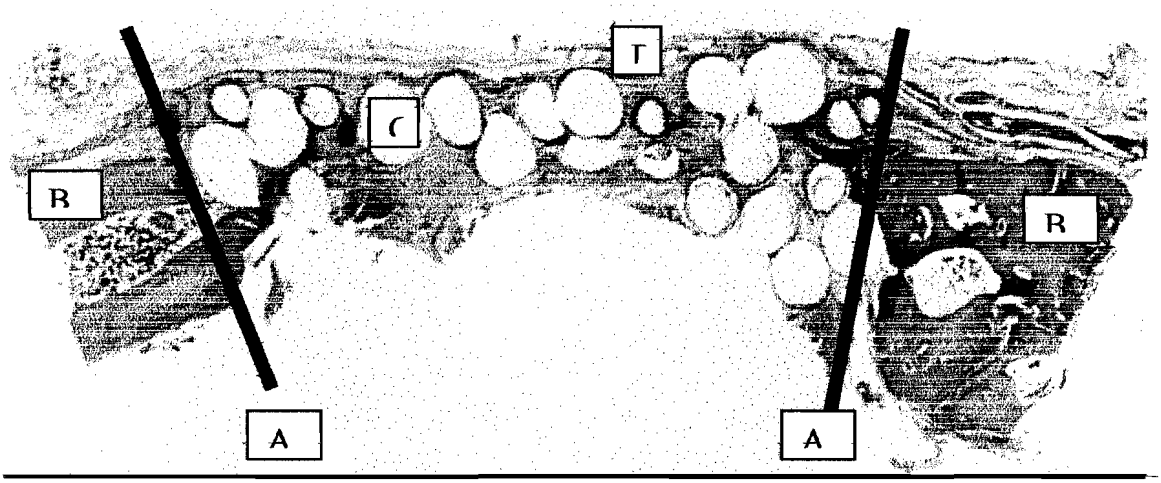
A. Suture line completely closed
B. Severe inflammation and necrosis of soft tissue evident by red coloring and cratering of tissue inward.

Picture 4. Adverse Healing – Brain of Test Animals



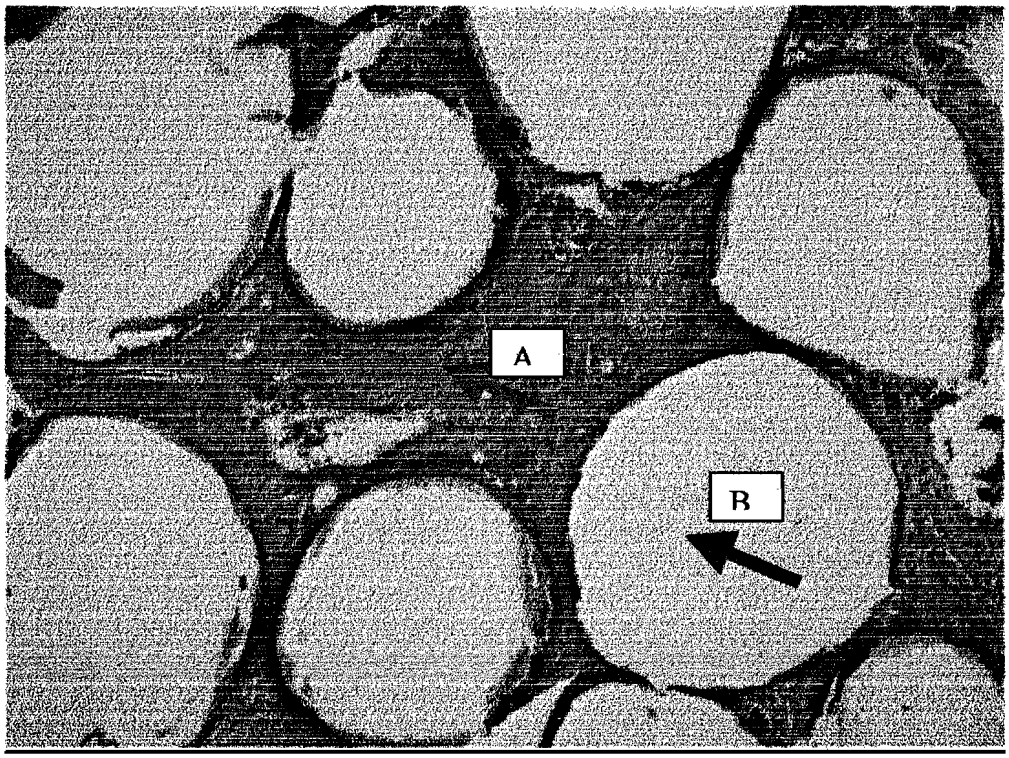
A. Bilateral areas of brain tissue in direct contact with the LC materials.

Picture 5. Histology-HTR (Positive Control) at 10 X



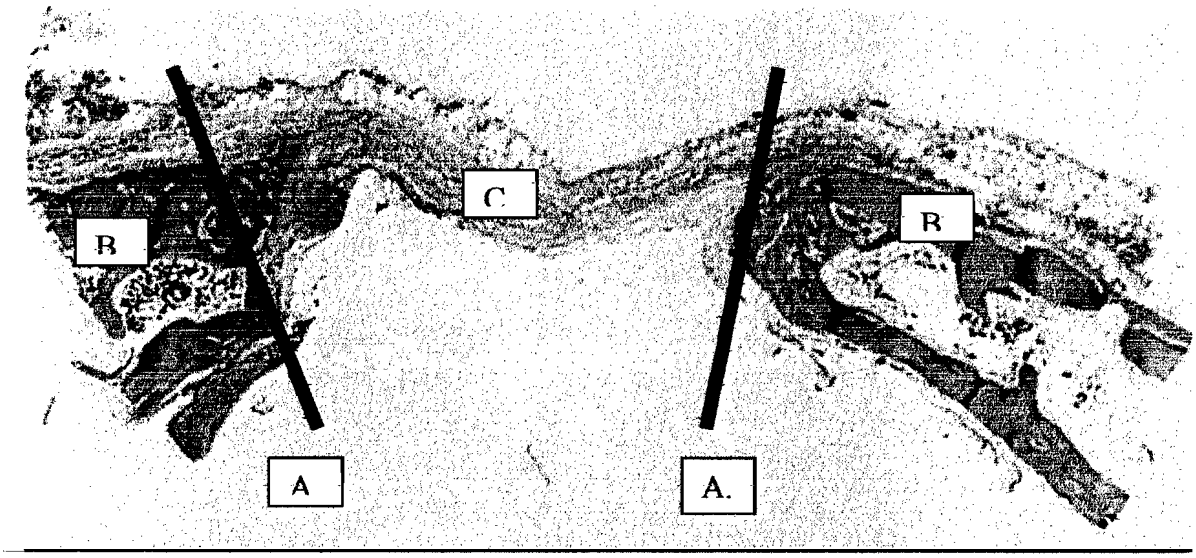
A. Black lines indicate the lateral borders of our defect.
B. Native bone
C. HTR particle space after processing.
D. Connective tissue bridging defect gap with some new bone present.

Picture 6. Histology-HTR (Positive Control)



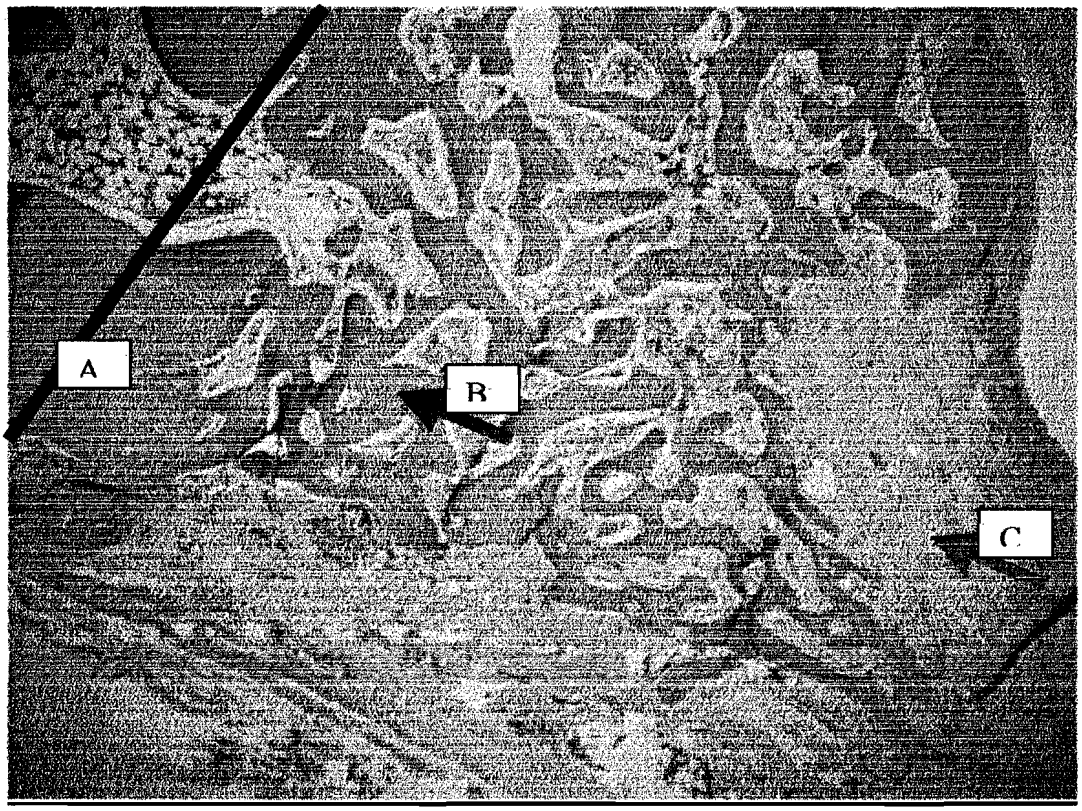
A. The green arrow indicates the HTR particle space after processing.
B. The blue arrow indicates connective tissue bridging between the HTR particles.

Picture 7. Histology – Ungrafted (Negative Control)



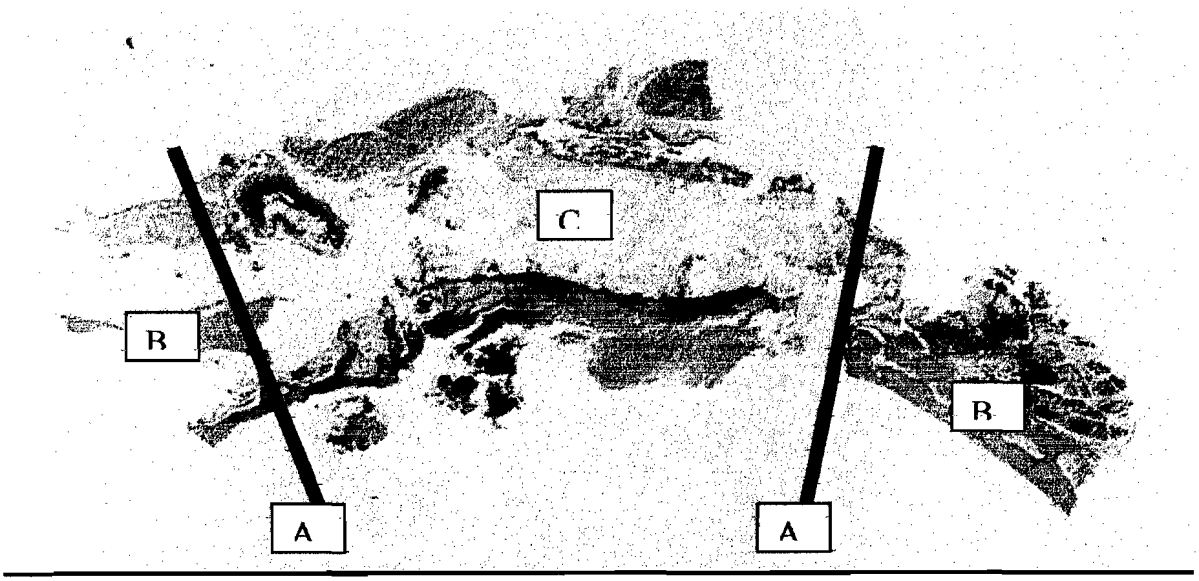
A. Black lines indicate the lateral borders of our defect.
B. Host native bone.
C. Connective tissue bridging the gap of defect.

Picture 8. Histology – Ungrafted (Negative Control)



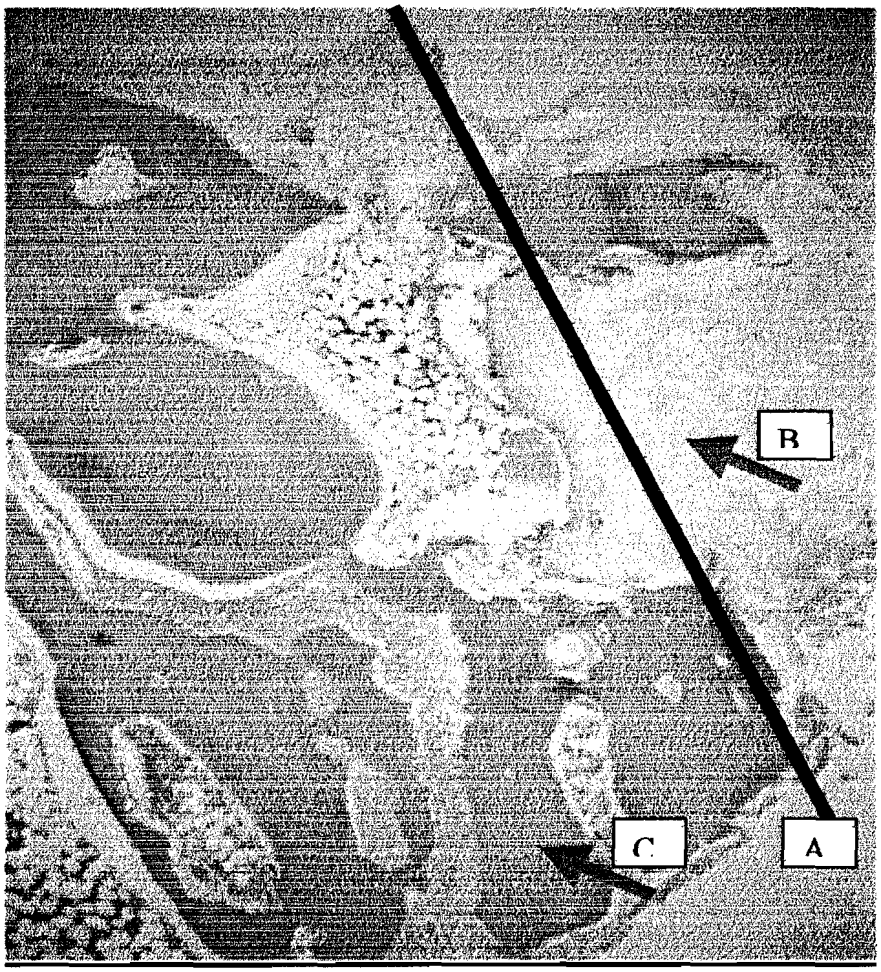
A. Black line indicates the lateral border of our defect.
B. The green arrow indicates new bone formation within the defect.
C. The blue arrow indicates the connective tissue bridging across the defect.

Picture 9. Histology – LC Test Material



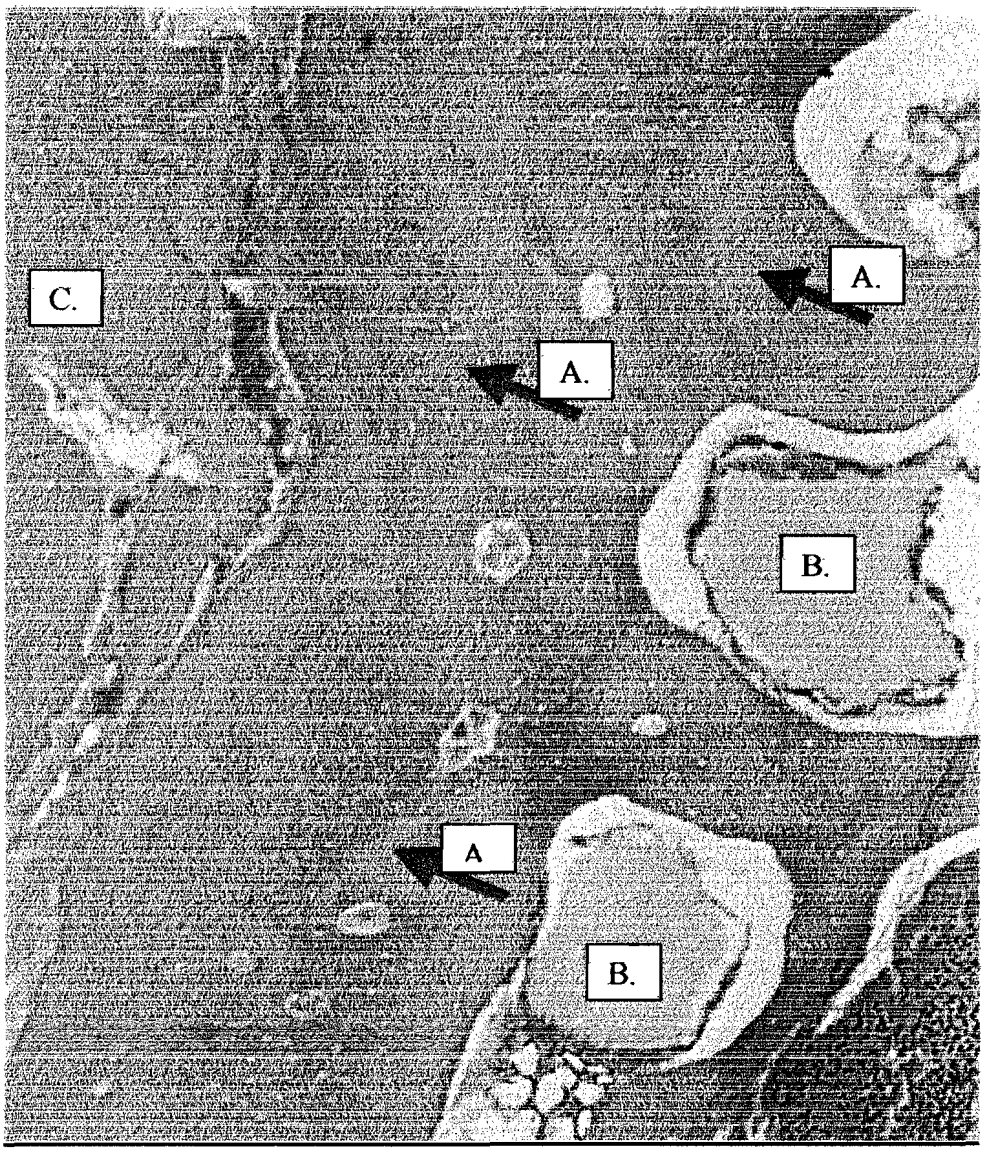
A. Black lines indicate the lateral borders of our defect.
B. Host native bone.
C. LC material in defect.

Picture 10. Histology – LC Test Material



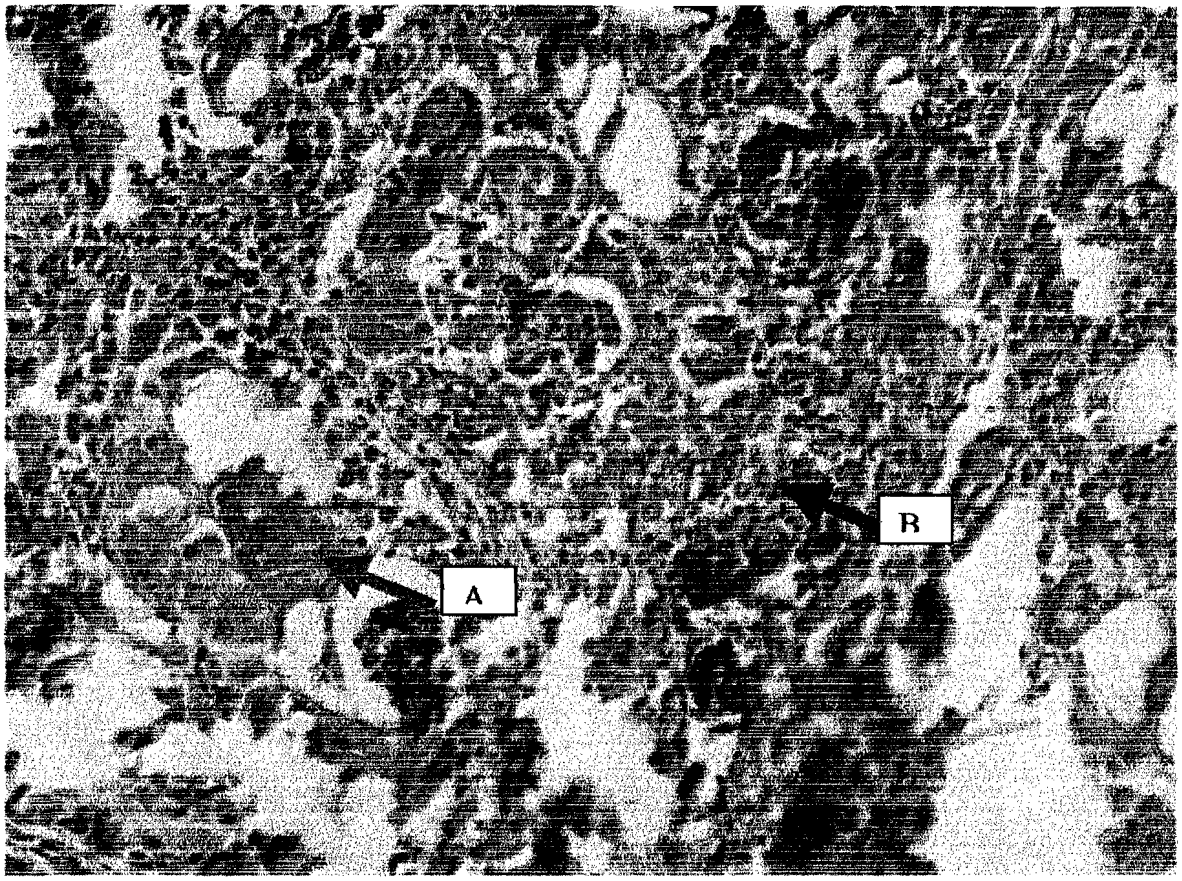
A. Black line indicates the lateral border of our defect.
B. The green arrow points to our test material.
C. The blue arrow points to necrotic bone adjacent to the test graft material.

Picture 11. Histology – LC Test Material



A. The blue arrows indicate necrotic bone, without nuclei present adjacent to the material.
B. LC material particles.
C. Uneffected host bone distant to the LC material.

Picture 12. Histology – LC Test Material

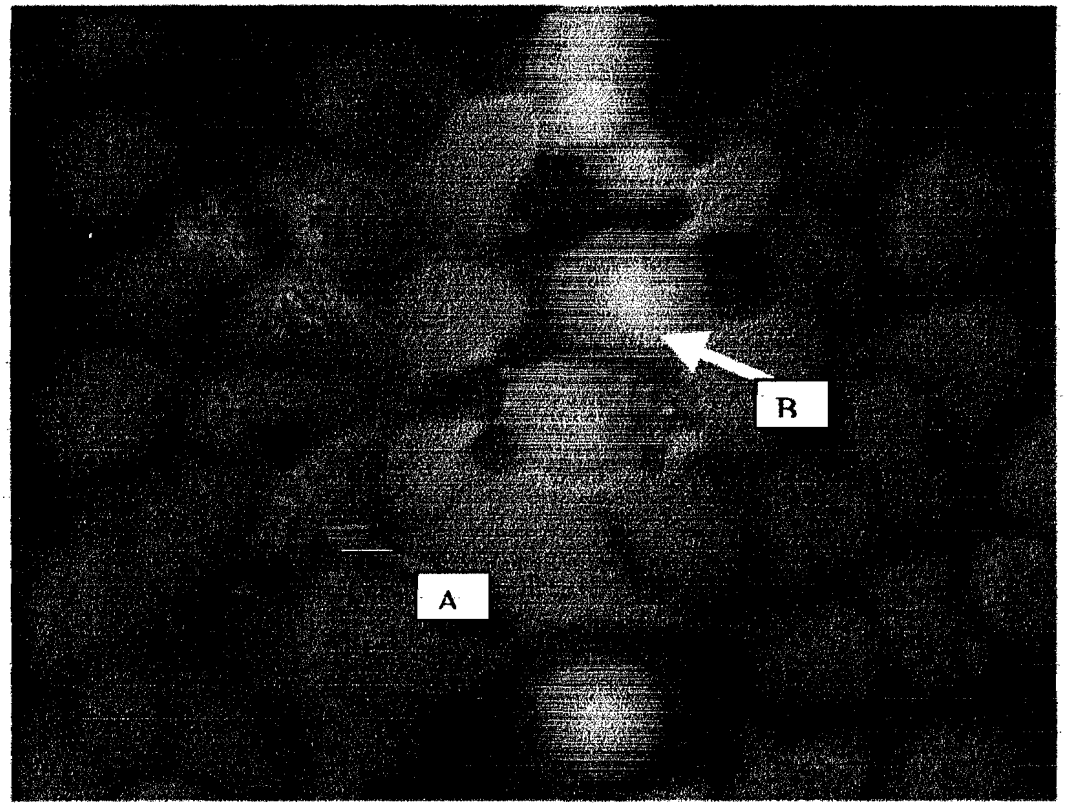


Section adjacent to test material.

A. The blue arrow indicates a multinucleated giant cell engulfing test material particles.

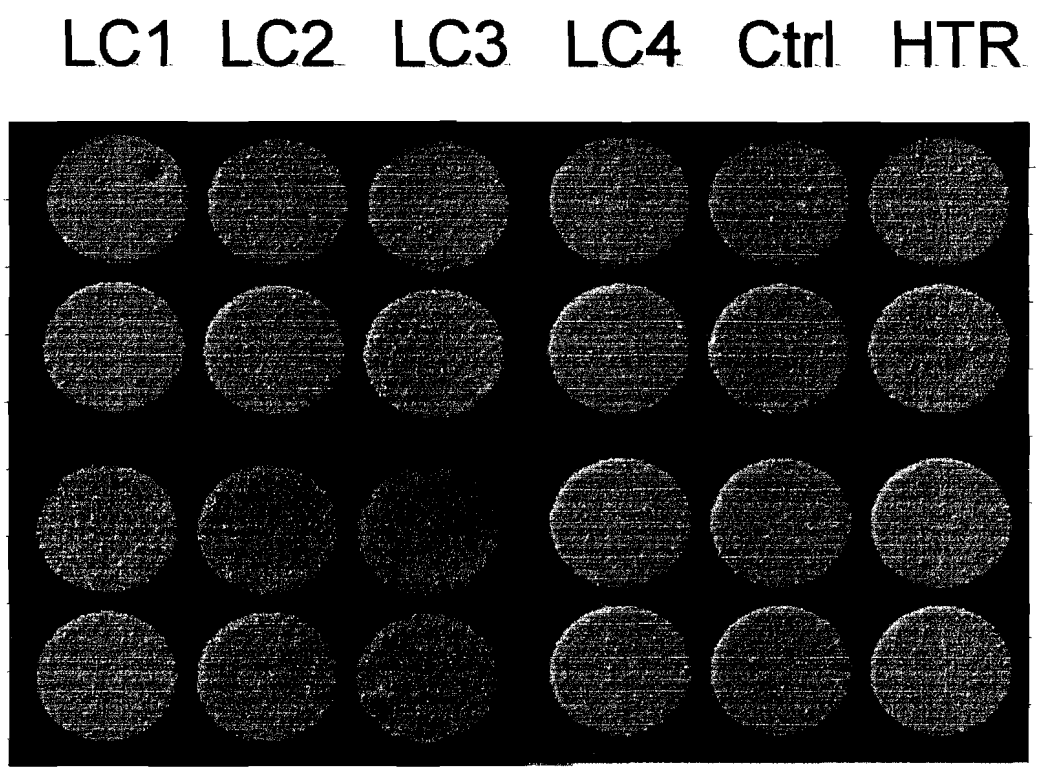
B. The green arrow indicates dense inflammatory cell infiltrate.

Picture 13. Immunofluorescence example



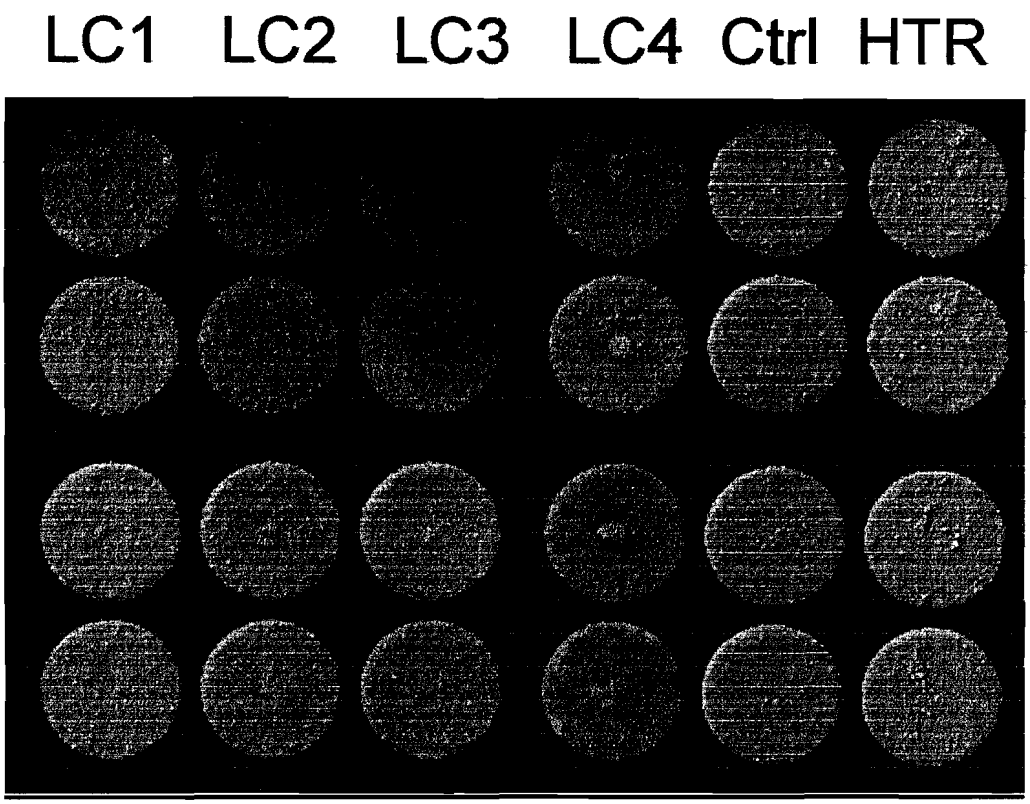
A. Blue arrow indicates Calcein (live cells)
B. Yellow arrow indicates Ethidium Homodimer (dead cells) immunofluorescence by manufacturer.

Picture 14. In vitro assay at 0 time point



No cell death as shown by uniform green (calcein) plates for all material types.

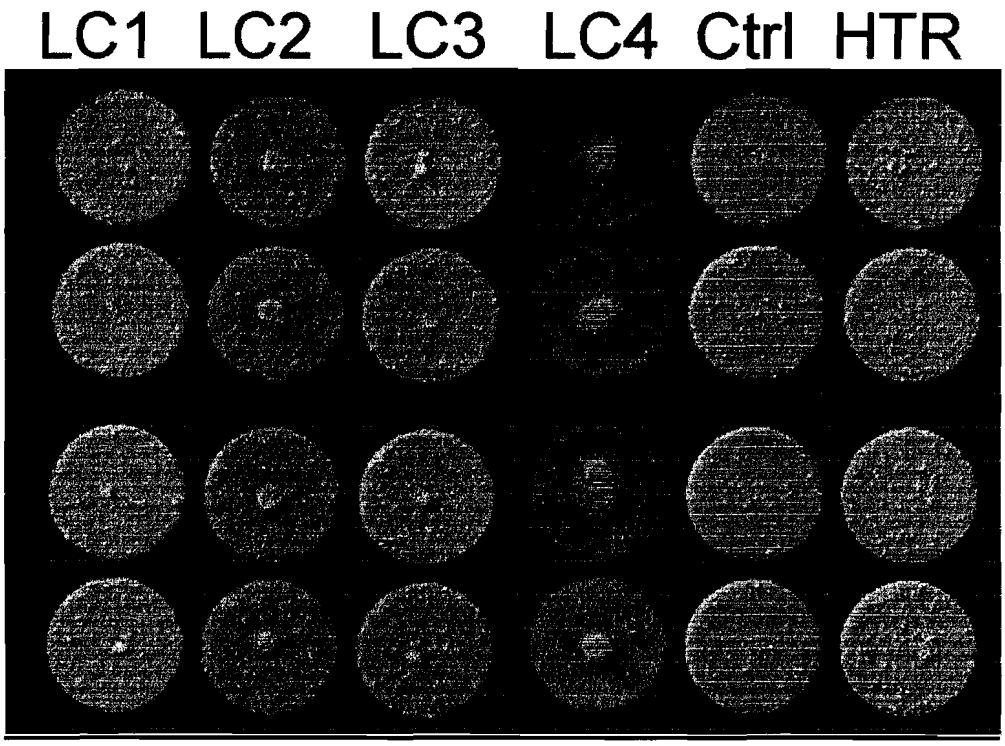
Picture 15. In vitro assay at 2 Hours



A. A.

A. LC-2 and LC-4 show areas of UMR death in direct contact with test material as indicated by the Ethidium Homodimer (red) within the field of Calcein (green).

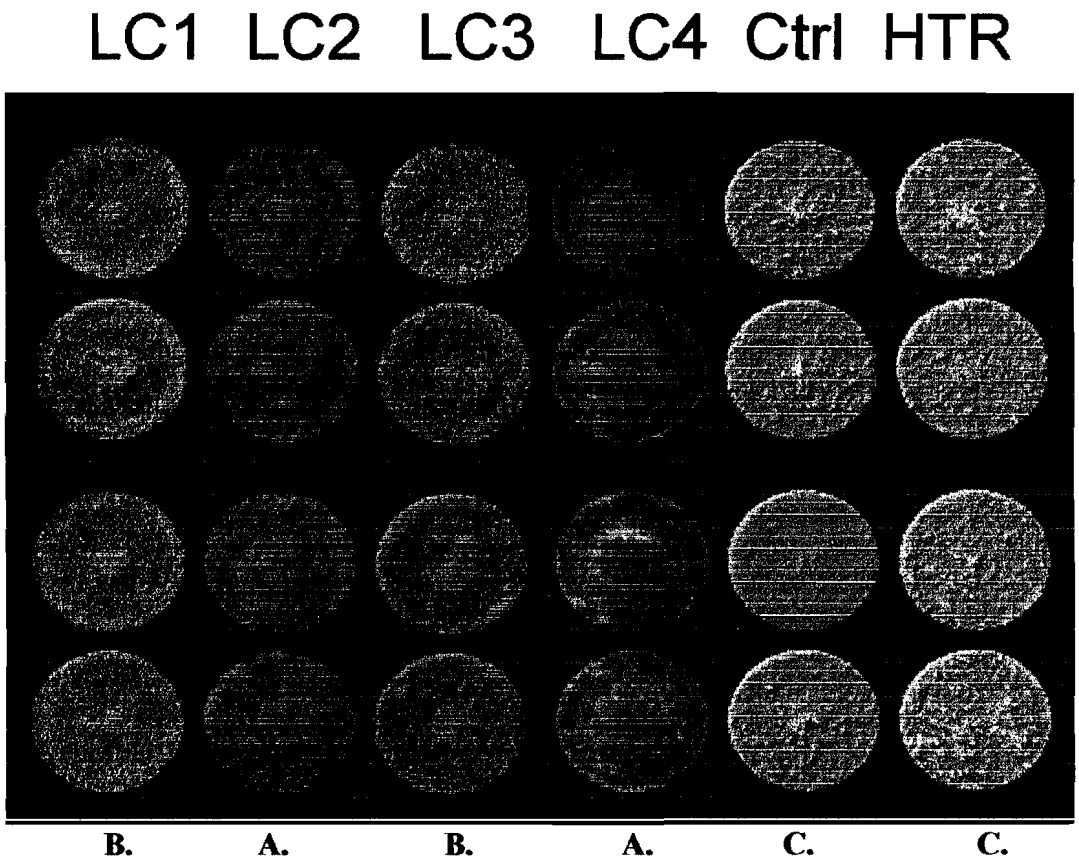
Picture 16. In vitro assay at 6 Hours



C. *B.* *C.* *A.* *C.* *C.*

A. **LC-4 shows severe lateral spread of UMR cell death indicated by the increase in Ethidium Homodimer (red) and the darkening of the entire plate.**
B. **LC-2 shows continuing lateral spread of UMR cell death but to a lesser extent than LC-4.**
C. **LC-1, LC-3, HTR, and no graft remain constant with no further UMR cell death.**

Picture 17. In vitro assay at 48 Hours



A. LC-2 and LC-4 show cell death over entire plate.
B. LC-1 and LC-3 show increasing cell death spreading laterally to the material.
C. HTR and no graft show no change.

Bibliography

EXHIBIT J

FIG # 1

GROSS SPECIMENT

1 - HTR-PLH

2 - DEFECT TIBIA ± 8MM

3 - HTR PARTICLE

4 - NEW BONE

FIG #2

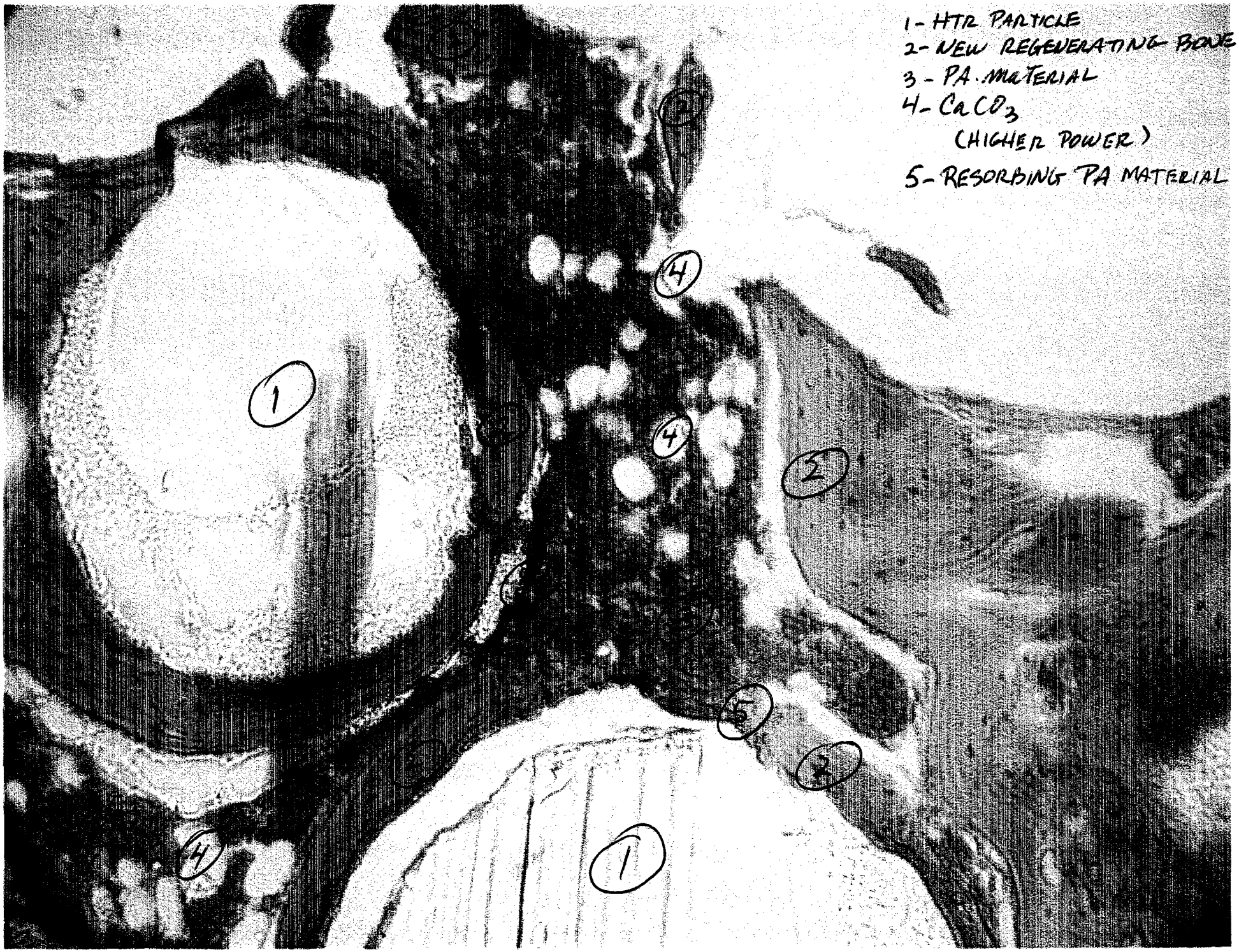
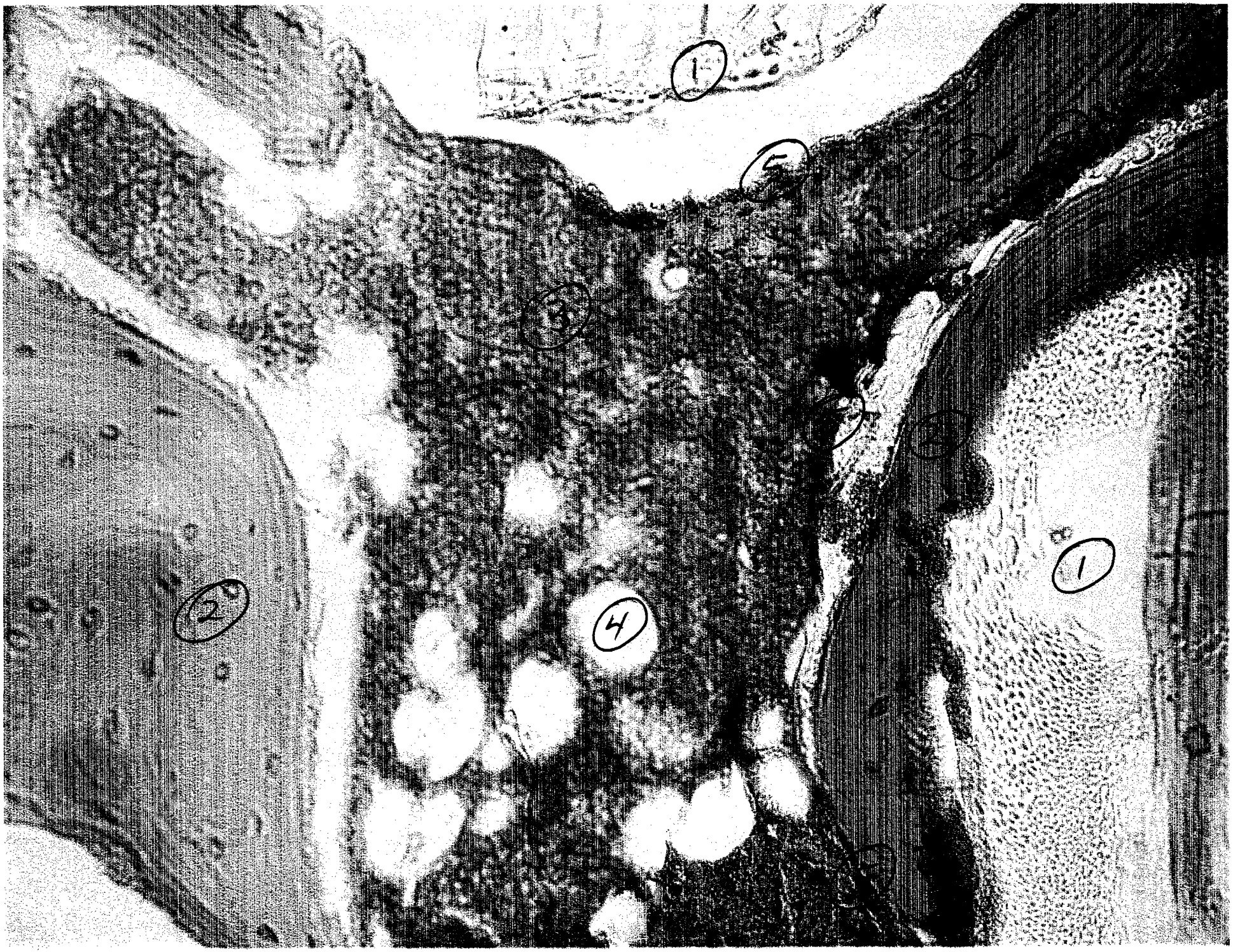

1- HTR PARTICLE
2- NEW REGENERATING BONE
3- PA. MATERIAL
4- $CaCO_3$
(HIGHER POWER)
5- RESORBING PA MATERIAL
1
2
4
4
2
5
2
1
4

FIG #3



beg. #4

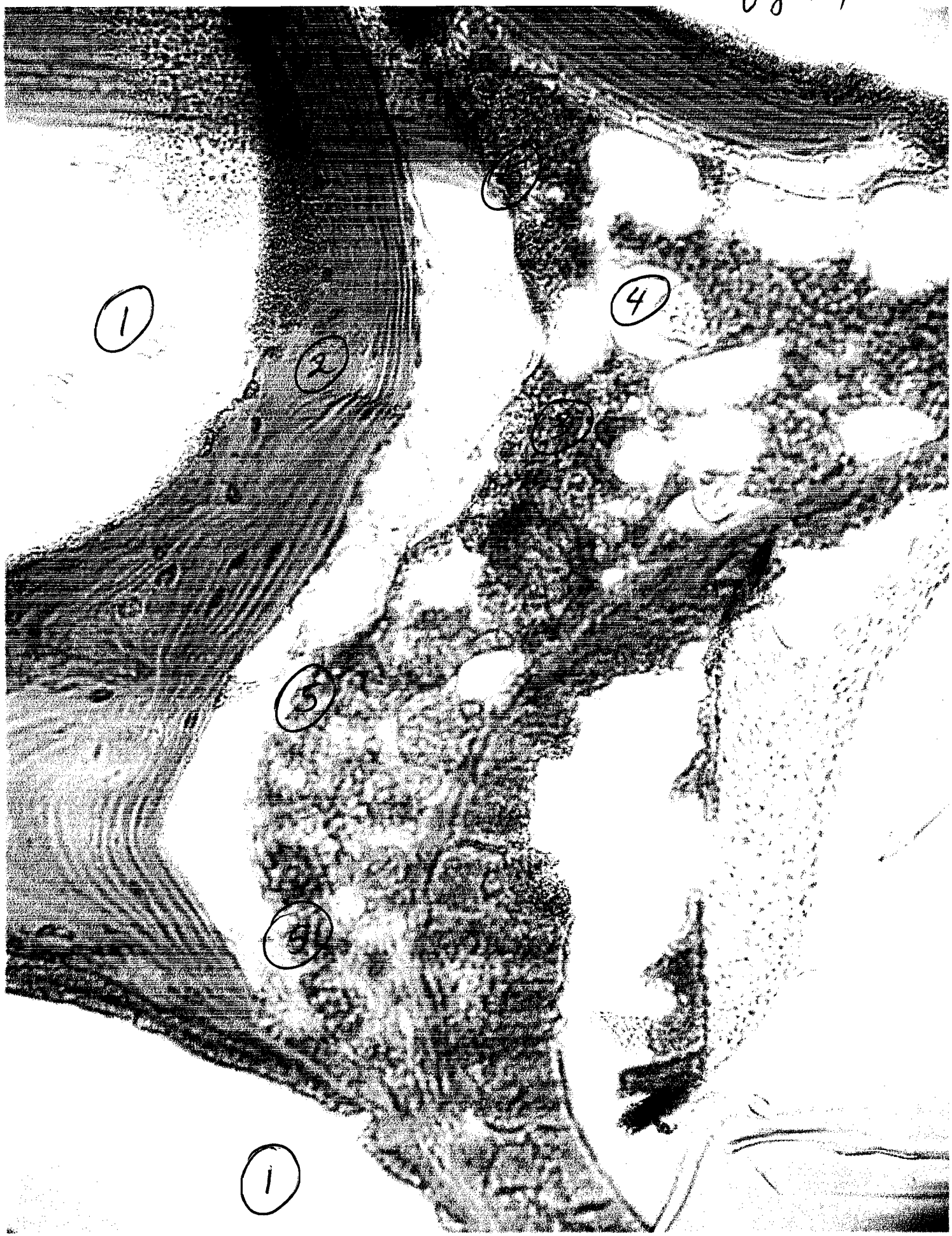
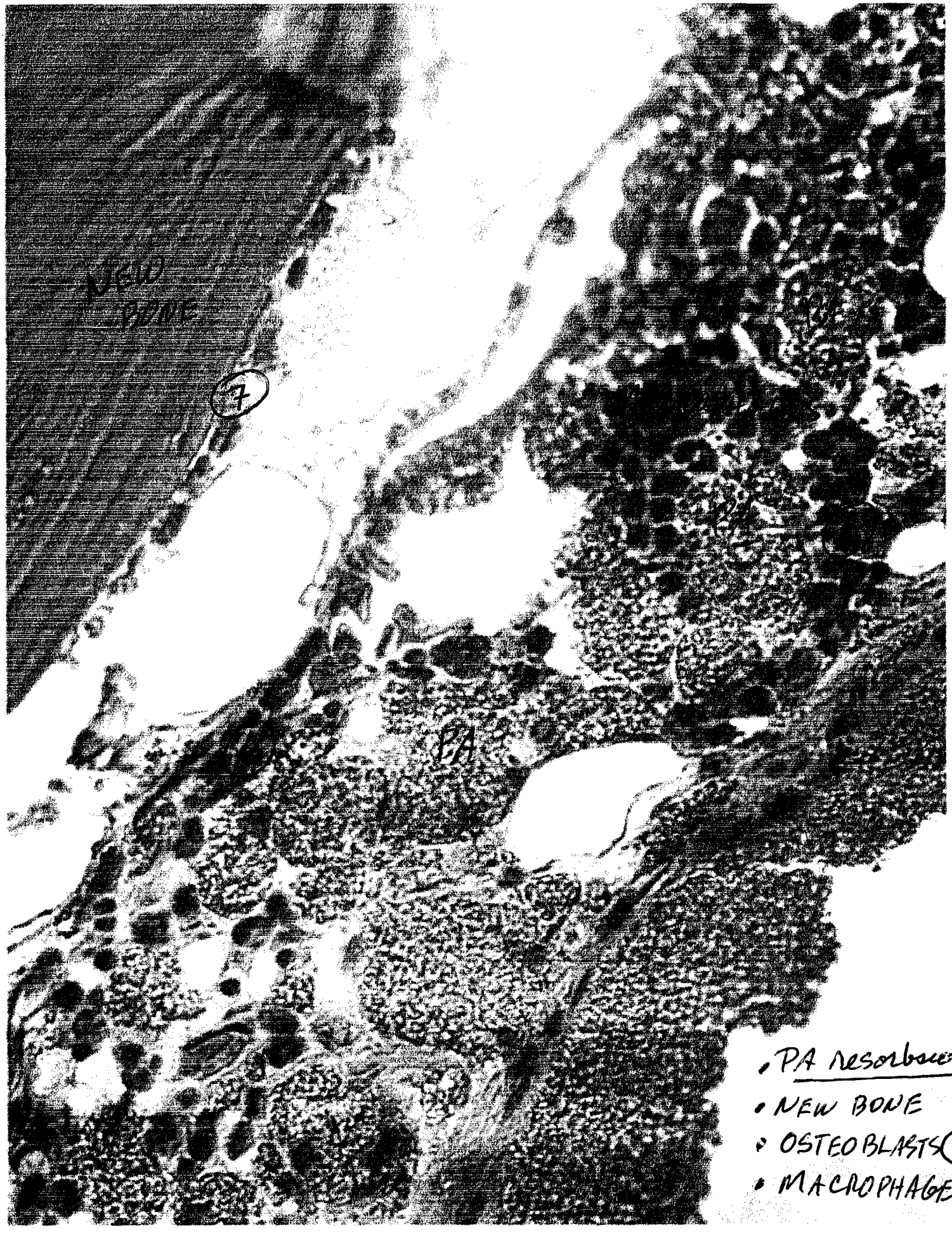
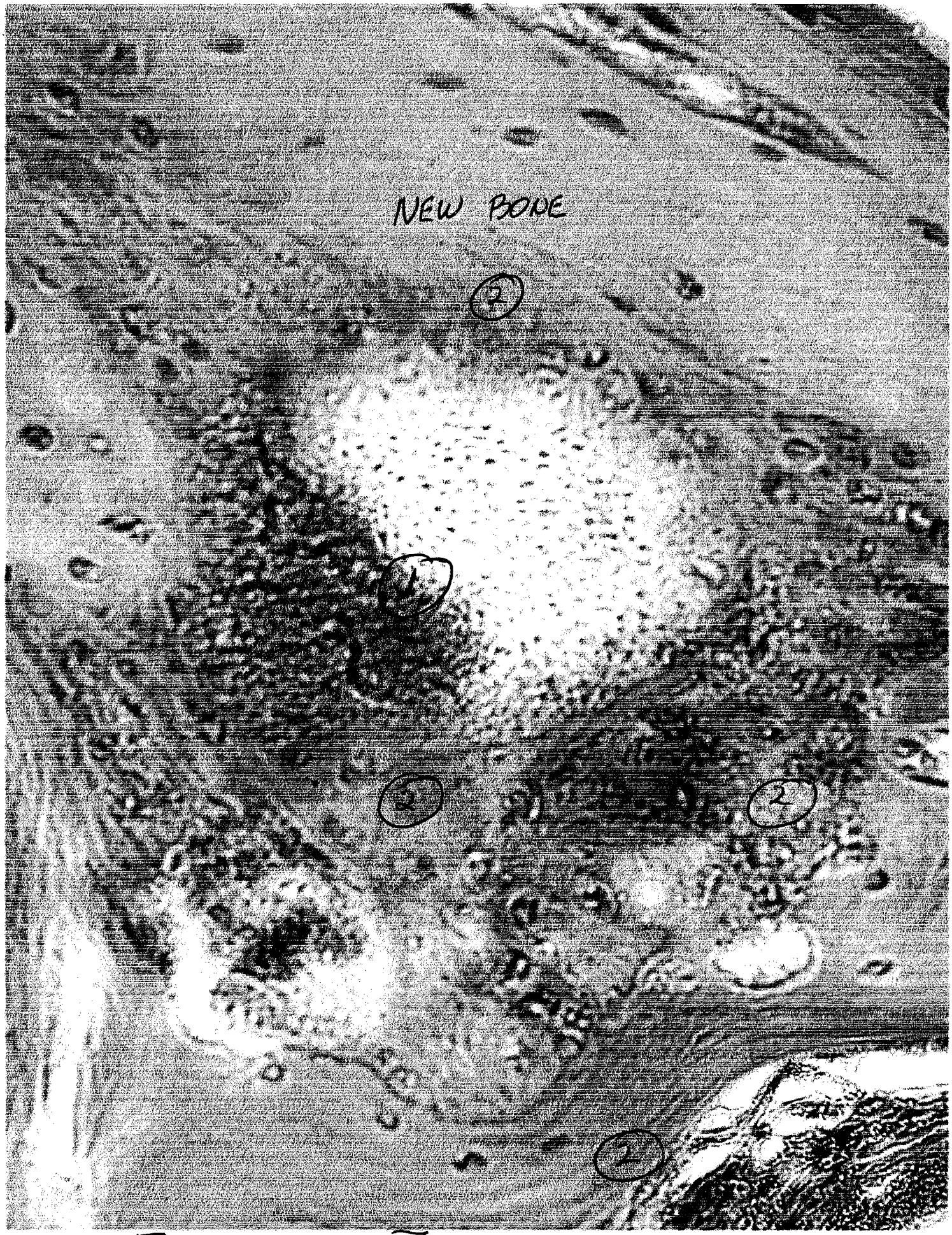


FIG # 5



- PA resorbcion
- NEW BONE
- OSTEOBLASTS (7)
- MACROPHAGES

FIG. #6



1 PA RESORPTION 2 NEW BONE FORMATION

FIG #7

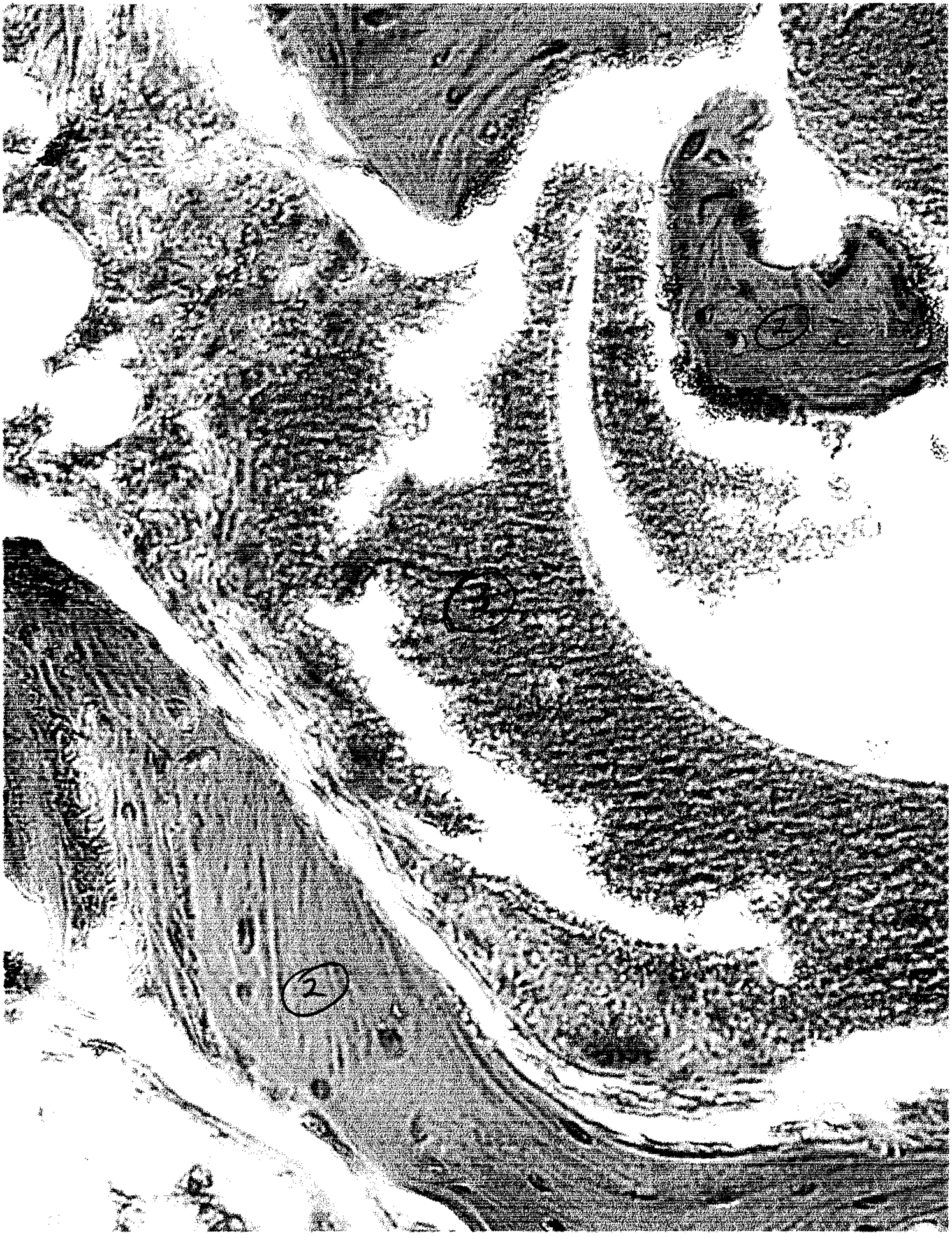


FIG. #8

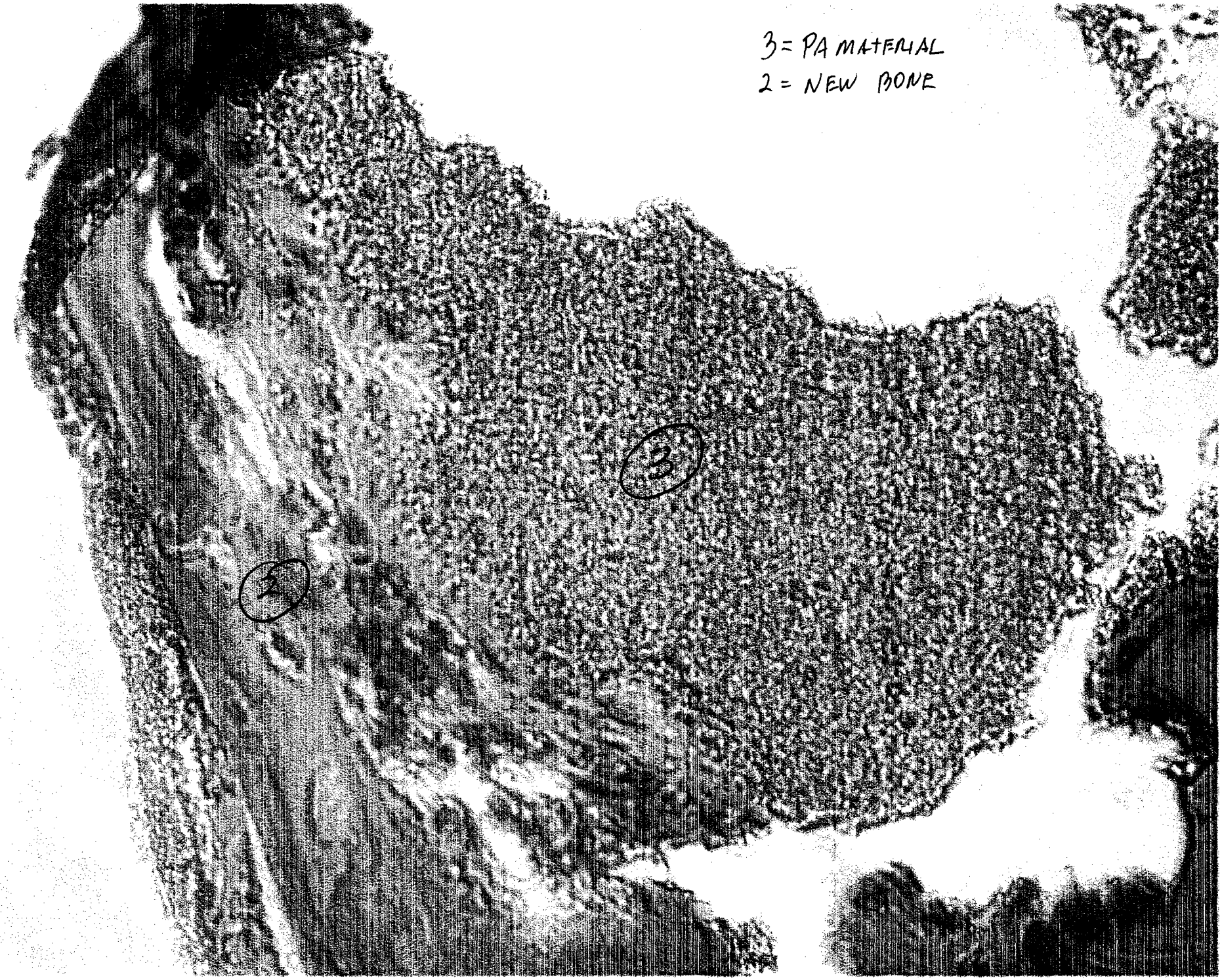


EXHIBIT K

US 20060052471A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2006/0052471 A1**

Ashman et al. (43) **Pub. Date: Mar. 9, 2006**

(54) **INITIATORS AND CROSSLINKABLE POLYMERIC MATERIALS**

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(21) Appl. No.: **11/240,747**

(22) Filed: **Sep. 30, 2005**

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/789,442, filed on Feb. 26, 2004.

(60) Provisional application No. 60/450,538, filed on Feb. 27, 2003.

Publication Classification

(51) **Int. Cl.**
C08F 2/46 (2006.01)

(52) **U.S. Cl.** **522/7**

(57) **ABSTRACT**

The present invention relates to novel initiator systems, methods of use, and cured composition for dental, orthopedic and drug delivery purpose. Specifically, it relates to a crosslinkable prepolymer where crosslinking is initiated by a two part system and a composition comprising an admixture of a resorbable bone substitute and a crosslinkable prepolymer. It also relates to the composition formed by crosslinking the admixture and a delivery system for crosslinking the polymer.

Figure 1A

Figure 1B

Figure 2A

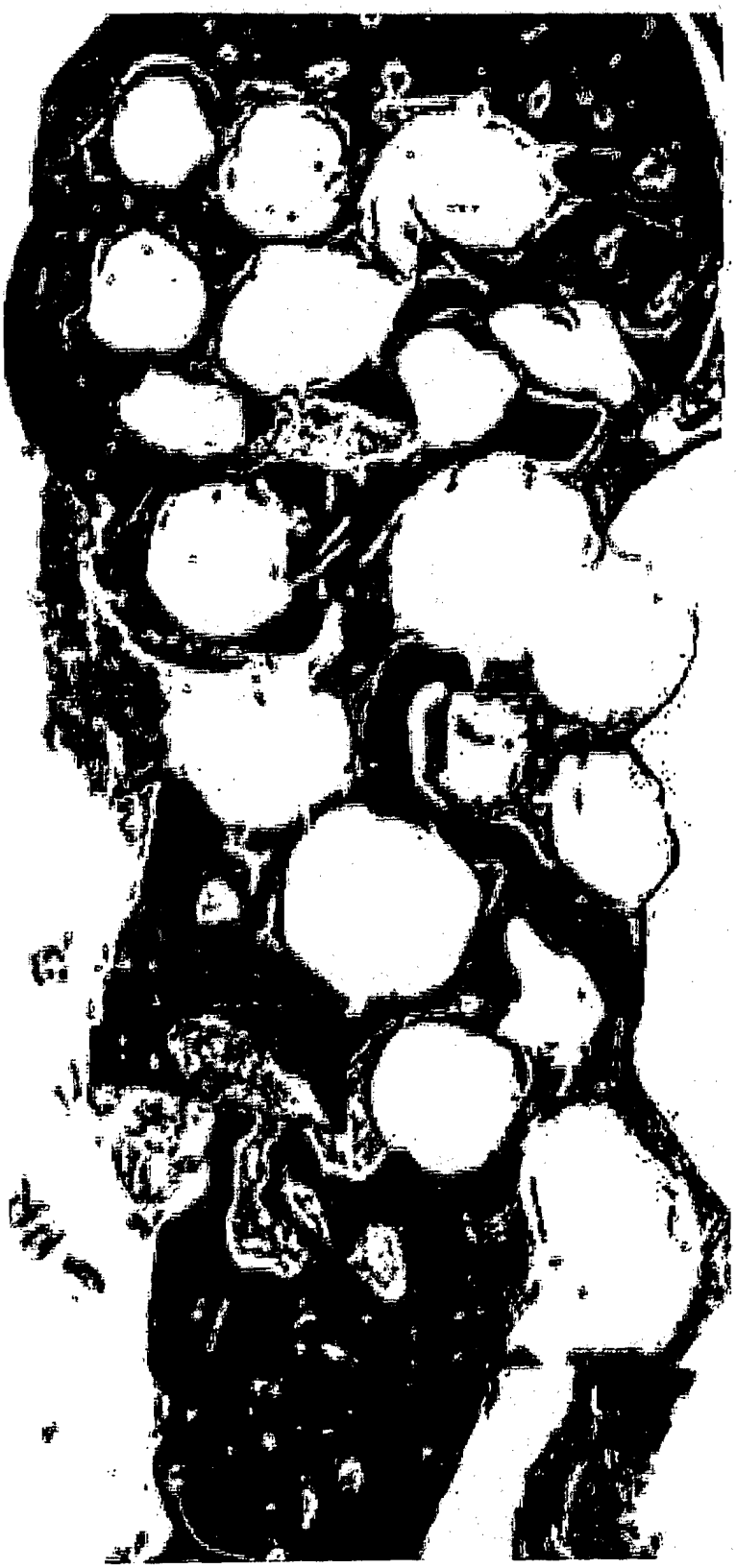


Figure 2B

INITIATORS AND CROSSLINKABLE POLYMERIC MATERIALS

[0001] This application claims priority to U.S. patent application Ser. No. 10/789,442 filed Feb. 26, 2004, herein incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates generally to initiators, methods of use, and materials which may be used in any part of the body as an implant or graft material. Specifically, the invention relates to initiators for crosslinkable polymeric materials which can promote the formation of bone and/or other tissue(s) and the applications for such materials.

BACKGROUND OF THE INVENTION

[0003] In the healing arts, there is often a need for an implant or graft material to replace, repair, or reconstruct tissues, in particular, hard tissues such as bone. For example, hard-tissue implant materials have been used in medicine and veterinary medicine as prosthetic bone materials to repair injured or diseased bone. Hard tissue implant materials are also used in the construction of prosthetic joints to fix the prosthetic joints to bones. In the dental art, hard tissue implant materials are used in the reconstruction of jaw bone damages caused by trauma, disease, or tooth loss; in the replacement or augmentation of the edentulous ridge; in the prevention of jaw bone loss by socket grafting; and in the treatment of periodontal bone void defects.

[0004] In orthopedics, hard tissue implant materials are used in the reconstruction of bone structure caused by trauma, disease, or surgery. For surgical procedures such as intervertebral diskectomy, the intervertebral disk is removed to provide access in removing the offending tissue, or bone osteophytes. In a spinal fusion procedure, it may be required to fix the vertebrae together to prevent movement and maintain a space originally occupied by the intervertebral disk.

[0005] During a spinal fusion following a diskectomy, a prosthetic implant or spinal implant is inserted into the intervertebral space. This prosthetic implant is often a bone graft material removed from another portion of the patient's body, termed an autograft. The use of bone taken from the patient's body has the important advantage of avoiding rejection of the implant, but has several shortcomings. There is always a risk in opening a second surgical site in obtaining the implant, which can lead to infection or pain for the patient, and the site of the implant is weakened by the removal of bony material. The bone implant may not be perfectly shaped and placed, leading to slippage or absorption of the implant, or failure of the implant to fuse with the vertebrae.

[0006] Other options for a graft source of the implant are bone removed from cadavers, termed allograft, or from other species, termed a xenograft. In these cases while there is the benefit of not having a second surgical site as a possible source of infection or pain, there is increased difficulty of the graft rejection and the risk of transmitting communicable diseases.

[0007] An alternative approach is using a bone graft or to use a manufactured implant made of a synthetic material that is biologically compatible with the body and the vertebrae. Over the last decade, polymeric materials have been used widely as bone graft materials. These materials are bio-inert, biocompatible, can serve as a temporary scaffold to be replaced by host tissue over time, and can be degraded by hydrolysis or by other means to non-toxic products.

[0008] Using these materials, various prosthetic implants can be generally divided into two basic categories, namely, solid implants and implants that are designed to encourage bone ingrowth. Implants that promote natural bone ingrowth achieve a more rapid and stable arthrodesis. Often, these implants are filled with autologous bone prior to insertion into the intervertebral disk space and include apertures which communicate with openings in the implant, thereby providing a path for tissue growth between the vertebral end plate and the bone or bone substitute within the implant. In preparing the intervertebral disk space for a prosthetic implant, the end plates of the vertebrae are preferably reduced to bleeding bone to facilitate tissue growth within the implant.

[0009] A number of difficulties still remain with the many prosthetic implants currently available. While it is recognized that hollow implants which permit bone ingrowth in the bone or bone substitute within the implant is an optimum technique for achieving fusion, most of these devices have difficulty achieving this fusion, at least without the aid of some additional stabilizing device, such as a rod or plate. Moreover, some of these devices are not structurally strong enough to support the heavy loads applied at the most frequently fused vertebral levels, mainly those in the lower lumbar spine.

[0010] In the dental art, when a tooth is extracted, a large cavity is created in the alveolar bone. The alveolar bone begins to undergo resorption at a rate of 40-60% in 2-3 years, which continues yearly at a rate of 0.25% to 0.50% per year until death (Ashman A. et al., Prevention of Alveolar Bone Loss Post Extraction with Bioplant® HTR® Grafting Material. *Oral Surg. Oral. Med. Oral. Pathol.* 60 (2):146-153, (1985)). Shifting of the remaining teeth, pocket formation, bulging out of the maxillary sinus, poor denture retention, loss of vertical dimension, formation of facial lines, unaesthetic gaps between bridgework and gum are some of the undesirable consequences associated with such loss (Luc. W. J. Huys, Hard Tissue Replacement, *Dentist News*, (Feb. 15, 2002)). Such bone loss also creates a significant problem for the placement of dental implants to replace the extracted tooth. It has been reported in previous years that nearly 95% of implant candidates rejected were turned down because of inadequate height and/or width of the alveolar bone (Ashman A., Ridge Preservation, Important Buzzwords in Dentistry, *General Dentistry*, May/June, (2000)).

[0011] One proven technique for overcoming the bone and soft tissue problems associated with the extraction of the tooth is to fill the extraction site with a bone graft material (e.g., synthetic, bovine or cadaver derived), and cover the site with gum tissue (e.g., suturing closed) or a dental "bandage" (e.g., Biofoil® Protective Stripes) for a period of time sufficient for new bone growth. The cavity becomes filled with a mixture of the bone graft material acting as an osteoconductive scaffold for the newly regenerated/generated bone. When implant placement is desired, after a period of time sufficient to allow bone regeneration (or healing) in

the cavity, a cylindrical bore drill can prepare the former extraction site, and a dental implant can be installed in the usual manner.

[0012] The problem associated with such technique is that, with most bone graft materials (e.g., cadaver- and bovine-derived); the dental implant cannot be installed immediately and placed in function with a suitable crown after the tooth extraction. Patients need to have repeated visits to the dentist's office, often waiting up to 6 months before a functional crown can be placed. In recent years, it has been reported that, with a few bone graft materials such as the Bioplant® HTR® detailed below, an implant can be placed immediately post-extraction (Ashman A. et al., Ridge Augmentation For Immediately Postextraction Implants: Eight-Year Retrospective Study, *The Regeneration Report,* 7(2), 85-95, (1995); Yukna R. A. et al., Evaluation of Hard Tissue Replacement Composite Graft Material as a Ridge Preservation/Augmentation Material in Conjunction with Immediate Hydroxyapatite-Coated Dental Implants, *J. Periodontol.*, pages 679-685, May 2003; and Yukna R. A. et al., Bioplant® HTR® Synthetic Bone Grafts and Immediate Dental Implants, *Compendium of Continuing Education in Dentistry*, pages 649-657, September 2003, 24(9)). However, such immediate post-extraction implants were not immediately made functional with a crown to chew. A healing period of 4-8 months was typically required for bone generation around the implant before loading. In other words, for example, prior to the present invention, if a patient has to have a front tooth extracted and replaced, the best the dentist can do is to install a metal implant (e.g., titanium) immediately after the extraction, place a bone graft material (e.g., Bioplant® HTR® or a "barrier membrane") around the implant in the socket and send him home. A crown cannot be installed on top of the metal implant until the implant becomes load-bearing (i.e., osteointegrated), months after the implant placement. In the meantime, the patient does not have a functional (e.g., cannot chew) or an esthetically-pleasing replacement tooth.

[0013] U.S. Pat. Nos. 4,535,485 and 4,536,158 disclose certain polymer-based implantable porous prostheses for use as bone or other hard tissue replacement which are composed generally of polymeric particles. Although the porous prostheses of the '485 and '158 patents have proven to be satisfactory for many applications in dentistry and orthopedics, there is room for improvement.

[0014] U.S. Pat. No. 4,728,570 discloses a porous implant material which induces the growth of hard tissue. Based on the '570 patent, Bioplant Inc. (South Norwalk, Conn.) manufactures a very slowly absorbable product called Bioplant® HTR® This product has proven to be very useful in both preventing bone loss and stimulating bone generation. It has also been found suitable for esthetic tissue plumping as well as for immediate post-extraction implants as mentioned above. However, it, like all bone graft materials prior to the present invention, when placed in an extraction socket or in edentulous spaces, the implant would not be immediately functional. A patient still must wait months for bone generation (e.g., osteointegration) to take place around the implant before revisiting the dentist's office months later to have a crown installed.

[0015] Within the last decade, polymers that are more biodegradable and/or bioresorbable than PMMA and PHEMA have been introduced into the field of tissue replacement.

[0016] Medical devices made with degradable polyesters such poly (L-lactic acid), poly(glycolic acid), and poly(lactic-co-glycolic acid) are approved for human use by the Food and Drug Administration, and have been used in many medical applications, for example, in sutures. These polymers, however, lack many properties necessary for restoring function in high load-bearing bone applications, since they undergo homogeneous, bulk degradation which is detrimental to the long-term mechanical properties of the material and leads to a large burst of acid products near the end of degradation (e.g., similar to inflammation). In contrast, surface eroding polymers (such as polyanhydrides) maintain their mechanical integrity during degradation and exhibit a gradual loss in size which permits bone ingrowth. However, linear polyanhydride systems have lirnited mechanical strength.

[0017] U.S. Pat. No. 5,837,752 discloses a semi-interpenetrating polymer network ("semi-IPN") composition for bone repair comprising (1) a linear polymer selected from the group consisting of linear, hydrophobic biodegradable polymers and linear non-biodegradable hydrophilic polymers; and (2) one or more crosslinkable monomers or macromers containing at least one free radical polymerizable group, wherein at least one of the monomers or macromers includes an anhydride linkage and a polymerizable group selected from the group consisting of acrylate or methacrylate.

[0018] U.S. Pat. No. 5,902,599 discloses biodegradable polymer networks which are useful in a variety of dental and orthopedic applications. Such biodegradable polymer networks can be formed by polymerizing anhydride prepolymers containing crosslinkable groups, such as unsaturated moieties. The anhydride prepolymers can be crosslinked, for example in a photopolymerization reaction by irradiation of the prepolymer with light in the presence of a photosensitive free radical initiator.

[0019] WO 01/74411 discloses a composition suitable for preparing a biodegradable implant comprised of a crosslinkable multifunctional prepolymer having at least two polymerizable terminal groups. It discloses placing a metal screw implant immediately into the extraction socket; firmly packing the void between the bone and the implant with a graft material such as the Bioplant® HTR®; applying a layer of the crosslinkable multifunctional prepolymer on top of the graft material and curing the layer to form a rigid collar around the metal implant. The cured ring around the neck of the implant allegedly resists the chewing forces on the implant that are mainly concentrated at the neck of the implant. However, the alleged support and resistance provided by such a cured ring is not sufficient in either the short or the long term, since the implant is only secured around the neck which is a very narrow area near the gum line. Hence, even if the cured ring is hardened, it does not provide adequate rigidity in the short term. In the long term, the cured ring does not have sufficient bone regenerating capability due to the lack of a bone stimulation material. Hence, the implant is not stable, still exhibits significant micromovement, and is not immediately load-bearing. Accord-

ingly, WO 01/74411 does not teach, suggest, or enable an immediately functional replacement tooth.

[0020] Therefore, there is a continued need in the replacement and restorative arts for materials and methods which reduce the time of the bone regenerative process, allow immediately functional dental implants, provide sufficient mechanical strength, and/or minimize micromovement. In addition, there is a need to broaden the spectra of materials available for dental and orthopedic implants and for bone substitutes that can be used for the delivery of therapeutic agents (i.e., bone growth factors).

SUMMARY OF THE INVENTION

[0021] The present invention relates to novel methods, compositions, and processes for dental, orthopedic and drug delivery purposes. Specifically, it relates to novel initiator systems, methods of use, and curable and cured composition for dental, orthopedic and drug delivery purpose. Specifically, it relates to a crosslinkable prepolymer where crosslinking is initiated by a two part system.

[0022] Surprisingly, it has been discovered that the foregoing invention provides a curable admixture which immediately hardens upon curing and which becomes load-bearing so as to provide immediate support for, e.g., the installation of a crown and immediate functionality for the artificial tooth or for the spine after spinal fusion.

[0023] The initiator system comprises (i) an initiator component having a light radical generating component, a chemical radical generating component, and a solvent, (ii) an accelerator component comprising: a light accelerator component, a chemical accelerator component, and a solvent, wherein the initiator system is useful for initiating polymerization of a crosslinkable anhydride polymer system.

[0024] In one embodiment, the composition also comprises a bone substitute, which can be a ceramic, alloplast, autograft, allograft, xenograft, or a mixture thereof. Preferably, it is an alloplast; more preferably a polymeric alloplast (porous or non-porous); even more preferably porous micron-sized particles, wherein each particle comprises a core layer comprised of a first polymeric material and a coating generally surrounding the core layer, the coating comprising a second polymeric material, wherein the second polymeric material is hydrophilic and has a composition different from the composition of the first polymeric material, and both polymeric materials are biocompatible.

[0025] Preferably, the diameter of the micron-sized particles is in the range of from about 250 microns to about 900 microns.

[0026] Preferably, the first polymeric material is polymethylmethacrylate, the second polymeric material is a polymeric hydroxyethylmethacrylate; and the composition further comprises a quantity of calcium hydroxide distributed on the internal and external surfaces of the micron-sized particles of the bone substitute. Upon exposure to aqueous solution (e.g., blood), calcium hydroxide is converted to a calcium carbonate apatite (bone) compound.

[0027] The crosslinkable prepolymer comprises a monomer and/or oligomer having polymerizable group(s) to crosslink to form a polymer network.

[0028] There are three embodiments detailed for the crosslinkable prepolymer, with the first two being the most preferred. When cured, the hydrophobic nature of the polyanhydrides and the crosslinked structure keep water out of the interior of the polymer and allow for hydrolysis only at the surface. Hence, the polymer erodes only from the outside in. This type of degradation is particularly beneficial for dental, orthopedic and drug delivery applications because the cured composite will maintain structural integrity and/or mechanical integrity. In comparison, the polyorthoesters and polyacetals, etc., disclosed in the third embodiment below tend to degrade in a more homogeneous fashion because they are more hydrophilic, not as tightly crosslinked, and more susceptible to water penetration. The biodegradable bonds in the third embodiment, therefore, cleave internally as well as externally, leading to a more rapid loss in strength at the outset.

[0029] Optionally, the composition further comprises a therapeutic agent, a bone promoting agent, a porosity forming agent, or a diagnostic agent.

[0030] The curable admixture comprising the bone substitute and the crosslinkable prepolymer or the crosslinkable semi-IPN precursor is cured to form a cured composite.

[0031] The curable admixture and the cured composite are useful in the field of orthopedics, dentistry, and drug delivery. They can be used anywhere where bone or other tissue regeneration is required. When a therapeutic agent is incorporated in them, they are useful as drug delivery devices.

DESCRIPTION OF THE DRAWINGS

[0032] **FIG. 1A** represents defects in the tibia at 8 weeks after treatment with a control.

[0033] **FIG. 1B** represents defects in the tibia at 8 weeks after treatment with a cured bone substitute containing Bioplant® HTR®.

[0034] **FIG. 2A** represents defects in the zygoma at 8 weeks after treatment with a control.

[0035] **FIG. 2B** represents defects in the zygoma at 8 weeks after treatment with a cured bone substitute containing Bioplant® HTR®.

DETAILED DESCRIPTION OF THE INVENTION

[0036] The present invention relates to a polymerization initiators and cured polymers. The present invention also relates to methods of forming and using the curable admixture and cured composite.

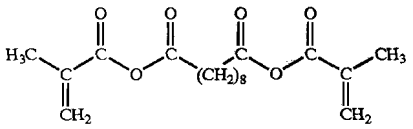
[0037] The cured composite is formed by crosslinking the curable admixture. The curable admixture is formed by mixing an optional bone substitute and a crosslinkable prepolymer to form a substantially homogeneous mixture. The admixture can be preformed or formed immediately before application.

Crosslinkable Anhydride Prepolymer

[0038] The crosslinkable anhydride prepolymer comprises monomers and/or oligomers having polymerizable groups, preferably radically polymerizable groups, which crosslink to form a polymer network. Suitable polymerizable groups include unsaturated alkenes (i.e., vinyl groups) such as vinyl

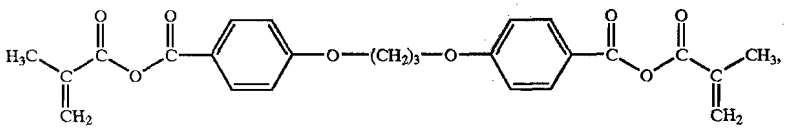
ethers, allyl groups, unsaturated monocarboxylic acids, unsaturated dicarboxylic acids, and unsaturated tricarboxylic acids. Unsaturated monocarboxylic acids include acrylic acid, methacrylic acid, and crotonic acid. Unsaturated dicarboxylic acids include maleic, fumaric, itaconic, mesaconic or citraconic acid. The preferred polymerizable groups are acrylates, diacrylates, oligoacrylates, dimethacrylates, oligomethacrylates, and other biologically acceptable polymerizable groups. (Meth)acrylates are the most preferred active species polymerizable group.

[0039] Methacrylated sebacic acid (mSA) is one preferred methacrylate. MSA has a low viscosity and degrades rapidly. MSA is described by:



[0040] and can be synthesized according to the procedure described by Tarcha et al. *J. Polym. Sci. Part A, Polym. Chem.* (2001), 39, 4189. MSA is particularly useful in the present invention, particularly when additional strength is necessary. Preferably, the composition will contain a buffer when mSA is used since mSA produces acid upon degradation. The addition of mSA to the composition also provides a decreased viscosity of the pre-polymerized formulations making the prepolymer more workable. It is added to improve mechanical properties of the cured polymer.

[0041] Methacrylated carboxyphenoxyalkanes (including propane (MCPP), hexane, (MCPH) etc) are another preferred methacrylate useful in the present invention. These compounds have higher viscosity than mSA and degrade more slowly. They are also more hydrophobic than mSA. MCPP, also abbreviated as CPPDM, is (1,3-bis(carboxyphenoxy))propyl dimethacrylate:



and can be synthesized according to the procedure described by Tarcha et al. *J. Polym. Sci, Part A, Polym. Chem.* (2001), 39, 4189.

[0042] Other polymerizable groups, including acrylates such as dimethylaminoethyl acrylate, cyanoacrylate, methyl methacrylate; N-vinyl pyrrolidone; poly(propylene fumerate); and methacrylic anhydride may also be used in a composition of the present invention.

[0043] These polymerizable groups can be present on hydrophobic or hydrophilic polymers, which can be used to adjust the hydrophobicity of the compositions. Non-limiting examples of suitable hydrophobic polymers include polyanhydrides, polyorthoesters, polyhydroxy acids, polydioxanones, polycarbonates, and polyaminocarbonates. Non-limiting examples of suitable hydrophilic polymers include synthetic polymers such as poly(ethylene glycol), poly(ethylene oxide), partially or fully hydrolyzed poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly-(ethylene oxide)-co-poly(propylene oxide) block copolymers (poloxamers and meroxapols), poloxamines, carboxymethyl cellulose (and derivatives), and hydroxyalkylated celluloses (and derivatives) such as hydroxyethyl cellulose and methylhydroxypropyl cellulose, and natural polymers such as polypeptides, polysaccharides or carbohydrates such as Ficoll® polysucrose, hyaluronic acid, dextran (and derivatives), heparan sulfate, chondroitin sulfate, heparin, or alginate, and proteins such as gelatin, collagen, albumin, or ovalbumin or copolymers or blends thereof. One preferred hydrophilic polymer is dimethacrylated poly(ethylene glycol) (PEGDM). More preferably, the molecular weight of the PEGDM will be a 300 or 600. The concentration of PEGDM in the prepolymer formulation is adjusted to obtain good workability and mixing properties of the prepolymer.

[0044] Preferably, the monomer and/or oligomer comprises a biodegradable linkage such as amide-, anhydride-, carbonate-, ester-, or orthoester linkages; more preferably, an anhydride-linkage so that the polymer network formed by the monomer and/or oligomer is biodegradable.

[0045] The molecular weight of the crosslinkable prepolymer is preferably in the range of about 150 to about 20,000. Preferably, the prepolymer has from 1 to about 100 repeating units in the structure, more preferably from about 1 to about 20, and most preferably from about 1 to about 10 repeating units.

[0046] Three non-limiting embodiments of the crosslinkable prepolymer are disclosed below.

[0047] Details of First Embodiment of Crosslinkable Prepolymer

[0048] As a first preferred embodiment, the crosslinkable prepolymer is one or more anhydride monomers or oligomers. Useful monomers or oligomers include anhydrides of a diacid or multifunctional acids and carboxylic acid molecules which include a crosslinkable group such as an unsaturated moiety.

[0049] Preferably, the crosslinkable prepolymer is linear with an unsaturated hydrocarbon moiety at each terminus and comprises a dianhydride of a dicarboxylic acid monomer or oligomer and a carboxylic acid molecule comprising an unsaturated moiety. More desirably, it comprises a methacrylic acid dianhydride of a monomer or oligomer of a diacid selected from the group consisting of sebacic acid and 1,3-bis(p-carboxyphenoxy)-alkane such as 1,3-bis(p-carboxyphenoxy)-propane.

[0050] Exemplary diacids or multifunctional acids include sebacic acid (SA), 1,3-bis(p-carboxyphenoxy)-alkanes such as 1,3-bis(p-carboxyphenoxy)-propane (CPP) or 1,3-bis(p-carboxyphenoxy)-hexane (CPH), dodecanedioic acid, fumaric acid, bis(p-carboxyphenoxy)methane, terephthalic acid, isophthalic acid, p-carboxyphenoxy acetic acid, p-carboxyphenoxy valeric acid, p-carboxyphenoxy octanoic acid, or citric acid. In one embodiment, it is preferably methacrylated sebacic acid (MSA), a methacrylated 1,3-bis(p-carboxyphenoxy)-alkane (e.g., MCPP or MCPH), or a combination thereof.

[0051] Exemplary carboxylic acids include methacrylic acid, or other functionalized carboxylic acids, including, e.g., acrylic, methacrylic, vinyl and/or styryl groups. The preferred carboxylic acid is methacrylic acid.

[0052] The anhydride monomers or oligomers are formed, for example, by reacting the diacid with an activated form of the carboxylic acid, such as an anhydride thereof, to form an anhydride. A detailed description of the anhydride monomer(s) or oligomer(s) suitable as crosslinkable prepolymer(s) is provided in the '599 patent, the specification of which is incorporated by reference in its entirety.

[0053] Another route for synthesizing the methacrylated sebacic acid (MSA) and (1,3-bis(carboxyphenoxy))propyl dimethacrylate (MCPP or CPPDM) is described by Tarcha, et al., *J. Polym. Sci, Part A, Polym. Chem.* (2001), 39, 4189.

[0054] In a preferred embodiment, the crosslinkable prepolymer is a mixture of a first anhydride and a second anhydride. The ratio of these anhydrides can be adjusted to provide the biodegradation, hydrophilicity and/or adherence properties most suitable for a specific application.

[0055] For example, polymer networks formed by crosslinking dimethacrylated anhydride monomers formed from sebacic acid typically biodegrade much faster than that formed from 1,3-bis(p-carboxyphenoxy)-alkane(s). Hence, mixing anhydrides formed from sebacic acid with anhydrides formed from 1,3-bis(p-carboxyphenoxy)-alkane(s) in various ratios provides a wide array of degradation behaviors.

[0056] In another example, where the polymer network is formed by crosslinking 1,3-bis(p-carboxyphenoxy)-alkane(s), methacrylic anhydride is added to increase plasticity and aid in mixing. Preferably, 1-10 mol % is added. The amount of methacrylic anhydride is dependent upon the consistency of the mixture (i.e., how much of an additional agent such as PEG is incorporated) and should be sufficient to allow for adequate mixing.

[0057] The ratio of the first anhydride to the second anhydride can vary widely. Preferably, it is in the range from about 1:20 to about 20:1; more preferably from about 1:5 to about 5:1; even more preferably from about 1:5 to about 1:1, most preferably at about 1:1.

[0058] Preferably, as detailed below, the crosslinkable prepolymer comprises a photoinitiator or a combination of a photoinitiator and a redox initiator system.

[0059] Details of Second Embodiment of Crosslinkable Prepolymer

[0060] In the second embodiment, the crosslinkable prepolymer is a crosslinkable semi-IPN precursor.

[0061] The crosslinkable semi-IPN precursor comprises at least two components: the first component is a linear polymer, and the second component is one or more crosslinkable monomers or macromers. The crosslinkable semi-IPN precursor forms a semi-interpenetrating network ("semi-IPN") when crosslinked. Semi-IPNs are defined as compositions that include two independent components, where one component is a crosslinked polymer and the other component is a non-crosslinked polymer. The crosslinkable semi-IPN precursor and the semi-IPN it forms are described in detail in U.S. Pat. No. 5,837,752 to Shastri et al., which is incorporated by reference in its entirety.

[0062] The first component of the crosslinkable semi-IPN precursor is a linear polymer. Preferably, the linear polymer in the first component is (i) a linear hydrophobic biodegradable polymer, preferably a homopolymer or copolymer which includes hydroxy acid and/or anhydride linkages, or (ii) a linear, non-biodegradable hydrophilic polymer, preferably polyethylene oxide or polyethylene glycol.

[0063] Preferably, at least one of the monomers or macromers includes a degradable linkage, preferably an anhydride linkage. The linear polymer preferably constitutes between 10 and 90% by weight of the crosslinkable semi-IPN precursor composition, more preferably between 30 and 70% of the crosslinkable semi-IPN precursor composition.

[0064] Linear polymers are homopolymers or block copolymers that are not crosslinked. Hydrophobic polymers are well known to those of skill in the art. Examples of suitable biodegradable polymers include polyanhydrides, polyorthoesters, polyhydroxy acids, polydioxanones, polycarbonates, and polyaminocarbonates. Preferred polymers are polyhydroxy acids and polyanhydrides. Polyanhydrides are the most preferred polymers.

[0065] Linear, hydrophilic polymers are well known to those of skill in the art. Examples of suitable hydrophilic non-biodegradable polymers include poly(ethylene glycol), poly(ethylene oxide), partially or fully hydrolyzed poly(vinyl alcohol), poly(ethylene oxide)-co-poly(propylene oxide) block copolymers (poloxamers and meroxapols) and poloxamines. Preferred hydrophilic non-biodegradable polymers are poly(ethylene glycol), poloxamines, poloxamers and meroxapols. Poly(ethylene glycol) is the most preferred hydrophilic non-biodegradable polymer.

[0066] The second component of the crosslinkable semi-IPN precursor is one or more crosslinkable monomers or macromers. Preferably, at least one of the monomers or macromers includes an anhydride linkage. Other monomers or macromers that can be used include biocompatible monomers and macromers which include at least one radically polymerizable group. For example, polymers including alkene linkages which can be crosslinked may be used, as disclosed in WO 93/17669 by the Board of Regents, University of Texas System, the disclosure of which is incorporated herein by reference.

[0067] Suitable polymerizable groups include unsaturated alkenes (i.e., vinyl groups) such as vinyl ethers, allyl groups, unsaturated monocarboxylic acids, unsaturated dicarboxylic acids, and unsaturated tricarboxylic acids. Unsaturated monocarboxylic acids include acrylic acid, methacrylic acid, and crotonic acid. Unsaturated dicarboxylic acids include maleic, fumaric, itaconic, mesaconic or citraconic acid. The preferred polymerizable groups are acrylates, diacrylates, oligoacrylates, dimethacrylates, oligomethacrylates, and other biologically acceptable polymerizable groups. (Meth-)acrylates are the most preferred active species polymerizable group. In one embodiment, the preferred methacrylate is a sebacic acid (MSA), a 1,3-bis(p-carboxyphenoxy)-alkane (e.g., MCPP or MCPH), or a combination thereof.

[0068] These functional groups can be present on hydrophobic or hydrophilic polymers, which can be used to adjust the hydrophobicity of the compositions. Suitable hydrophobic polymers include polyanhydrides, polyorthoesters, polyhydroxy acids, polydioxanones, polycarbonates, and polyaminocarbonates. Suitable hydrophilic polymers include synthetic polymers such as poly(ethylene glycol), poly(ethylene oxide), partially or fully hydrolyzed poly(vinyl alcohol), poly(vinylpyrrolidone), poly(ethyloxazoline), poly(ethylene oxide)-co-poly(propylene oxide) block copolymers (poloxamers and meroxapols), poloxamines, carboxymethyl cellulose, and hydroxyalkylated celluloses such as hydroxyethyl cellulose and methylhydroxypropyl cellulose, and natural polymers such as polypeptides, polysaccharides or carbohydrates such as Ficoll® polysucrose, hyaluronic acid, dextran, heparan sulfate, chondroitin sulfate, heparin, or alginate, and proteins such as gelatin, collagen, albumin, or ovalbumin or copolymers or blends thereof.

[0069] The polymers can be biodegradable, but are preferably of low biodegradability (for predictability of dissolution) but of sufficiently low molecular weight to allow excretion. The maximum molecular weight to allow excretion in human beings (or other species in which use is intended) will vary with polymer type, but will often be about 20,000 daltons or below.

[0070] The polymers can include two or more water-soluble blocks which are joined by other groups. Such joining groups can include biodegradable linkages, polymerizable linkages, or both. For example, an unsaturated dicarboxylic acid, such as maleic, fumaric, or aconitic acid, can be esterified with hydrophilic polymers containing hydroxy groups, such as polyethylene glycols, or amidated with hydrophilic polymers containing amine groups, such as poloxamines.

[0071] Methods for the synthesis of these polymers are well known to those skilled in the art. See, for example, Concise Encyclopedia of Polymer Science and Polymeric Amines and Ammonium Salts, E. Goethals, editor (Pergamen Press, Elmsford, N.Y. 1980). Many polymers, such as poly(acrylic acid), are commercially available. Naturally occurring and synthetic polymers may be modified using chemical reactions available in the art and described, for example, in March, "Advanced Organic Chemistry," 4th Edition, 1992, Wiley-Interscience Publication, New York.

[0072] Preferably, the monomers and/or macromers that include radically polymerizable groups include slightly more than one crosslinkable group on average per molecule, more preferably two or more polymerizable or crosslinkable groups on average per molecule. Because each polymerizable group will polymerize into a chain, crosslinked materials can be produced using only slightly more than one reactive group per polymer (i.e., about 1.02 polymerizable groups on average).

[0073] Details of Third Embodiment of Crosslinkable Prepolymer

[0074] The third embodiment of the crosslinkable prepolymer is disclosed in U.S. Pat. Pub. 2003/114552, the specification of which is hereby incorporated by reference in its entirety. Specifically, it is a crosslinkable multifunctional prepolymer comprising at least two polymerizable terminal groups and having a viscosity such that the crosslinkable prepolymer is deformable at a temperature of 0° to 60° C. into a three-dimensional shape and being crosslinkable within the temperature range. Preferably, the crosslinkable prepolymer comprises a hydrophilic region, at least one biodegradable region, and at least one polymerization region and has from 1 to about 100, more preferably from 1 to 20, most preferably 1 to 10, repeating units. The hydrophilic region preferably is a polyethylene glycol or a copolymer of ethylene oxide and an alkylene oxide with a degree of polymerization in the range of 2 to 500.

[0075] The crosslinkable prepolymer may comprise a polyacetal sequence; a polyester sequence, resulting from copolymerizing a mixture of lactones wherein none of the lactone co-monomers is present in the resulting polyester sequence in a molar proportion above 75%; or a polyorthoester sequence; or a combination of a polyester sequence and a polyorthoester sequence. The polymerizable region of the crosslinkable prepolymer contains alkenes, alkynes or both.

Initiator System

[0076] The present invention utilizes an initiator system to cure the crosslinkable prepolymer. In one embodiment, both light curing and chemical curing is used. The initiator system is divided into two parts, an initiator and an amine accelerator. The initiator (component A) comprising the light and chemical initiators and the amine accelerator (component B) comprising the light and chemical accelerators. This system allows for fast curing of the polymer from light curing, while the chemical curing initiates the crosslinking reaction throughout the polymer matrix and increases the viscosity so that the material sets homogeneously.

[0077] In one preferred embodiment, the two components are mixed with the crosslinkable prepolymer immediately before curing. In other embodiments, one of the components is mixed with a component of the polymer or monomer or with the filler component prior to curing (e.g. to form a kit that can be easily manipulated to crosslink the prepolymer. When the initiator is pre-mixed, care must be taken to combine components so as not to degrade the polymer or prepolymer (particularly where the polymer is an anhydride which can be unstable in the presence of an oxidant) or destroy the initiator.

Initiator—Component A

[0078] In a first embodiment, Component A comprises a light radical generating component activated by electromagnetic radiation, i.e., a photoinitiator. This may be ultraviolet light (e.g., long wavelength ultraviolet light), light in the visible region, focused laser light, infra-red and near-infrared light, X-ray radiation or gamma radiation. Preferably, the radiation is light in the visible region and, more preferably, is blue light. Exposure of the photoinitiator and a co-catalyst such as an amine to light generates active species. Light absorption by the photoinitiator causes it to assume a triplet state; the triplet state subsequently reacts with the co-catalyst to form an active species which initiates polymerization.

[0079] Non-limiting examples of the photoinitiators include biocompatible photoinitiators such as beta carotene, riboflavin, Irgacure 651® (2,2-dimethoxy-2-phenylacetophenone), phenylglycine, dyes such as erythrosin, phloxime, rose bengal, thonine, camphorquinone, ethyl eosin, eosin, methylene blue, riboflavin, 2,2-dimethyl-2-phenylacetophenone, 2-methoxy-2-phenylacetophenone, 2,2-dimethoxy-2-phenyl acetophenone, and other acetophenone derivatives, and camphorquinone. A preferred photoinitiator is camphorquinone.

[0080] Component A also comprises a second free radical generator (i.e., a chemical radical generator). The free radical generator is an oxidizing agent (also called an oxidizing component), such as peroxide. This agent is combined in a redox couple by mixing component A with component B, resulting in the generation of an initiating species (such as free radicals, anions, or cations) capable of causing curing. Preferably, the redox couples of this invention are activated at temperatures below about 40° C., for example, at room temperature or at the physiological temperature of about 37° C. The redox couple is partitioned into separate reactive components A and B prior to use and then subsequently mixed at the time of use to generate the desired initiating species. Selection of the redox couple is governed by several criteria. For example, a desirable oxidizing agent is one that is sufficiently oxidizing in nature to oxidize the reducing agent, but not excessively oxidizing that it may prematurely react with other components with which it may be combined during storage. Oxidation of the resin with an inappropriate oxidizing agent could result in an unstable system that would prematurely polymerize and subsequently provide a limited shelf life.

[0081] Suitable oxidizing agents include peroxide compounds (i.e., peroxy compounds), including hydrogen peroxide as well as inorganic and organic peroxide compounds (e.g., "per" compounds or salts with peroxoanions). Examples of suitable oxidizing agents include, but are not limited to: peroxides such as benzoyl peroxide, phthaloyl peroxide, substituted benzoyl peroxides, acetyl peroxide, caproyl peroxide, lauroyl peroxide, cinnamoyl peroxide, acetyl benzoyl peroxide, methyl ethyl ketone peroxide, sodium peroxide, hydrogen peroxide, di-tert butyl peroxide, tetraline peroxide, urea peroxide, and cumene peroxide; hydroperoxides such as p-methane hydroperoxide, di-isopropyl-benzene hydroperoxide, tert-butyl hydroperoxide, methyl ethyl ketone hydroperoxide, and 1-hydroxy cyclohexyl hydroperoxide-1, ammonium persulfate, sodium perborate, sodium perchlorate, potassium persulfate, ozone, ozonides, 2-hydroxy-4-methoxy-benzophenone, 2 (2-hydroxy-5-methylphenyl) benzotriazol etc. Benzoyl peroxide is the preferred oxidizing agent. Other oxidizing agents include azo initiators, such as azoisobutyronitrile (AIBN) or 2,2-azobis (2-amidopropane) dihydrochloride.

[0082] These oxidizing agents may be used alone or in admixture with one another. One or more oxidizing agents may be present in an amount sufficient to provide initiation of the curing process. Preferably, this includes about 0.01 weight percent (wt-%) to about 4.0 wt-%, and more preferably about 0.05 wt-% to about 1.0 wt-%, based on the total weight of all components of the dental material.

[0083] Thus, suitable redox couples individually provide good shelf-life (for example, at least 2 months, preferably at least 4 months, and more preferably at least 6 months in an environment of 5-20° C.), and then, when combined together, generate the desired initiating species for curing or partially curing the curable admixture. The shelf life of the photoinitiator is dependent on the exposure to light. It is therefore preferred to store component A in an opaque container and/or in the dark. It is also preferred to formulate A such that oxidizers in the formulation do not react with the other components in the mixture and thereby reduce the shelf life.

[0084] In one particular embodiment, component A contains camphorquinone (CQ) and benzoyl peroxide (BPO). Preferably, the relative amounts (w/w) are between 5:1 and 1:5, more preferably between 2:1 and 1:2, and desirably about 1:1.

[0085] The light and chemical radical generating components are preferably dissolved in a liquid such as a PEG, PEG methacrylate, or a PEG dimethacrylate. Ethyl acetate, acetone, N-methyl-pyrrolidone, and/or N-vinyl pyrrolidone may also be added. The liquid primarily acts as a solvent for the initiator component and can be selected dependent on the viscosity desired for the mixture. Some of the solvents will also polymerize upon curing, and be incorporated into the polymer matrix (i.e., a reactive polymer). It may contain a reactive or non-reactive polymer that can be both a solvent and part of the shell polymer matrix. In addition to being a solvent, the liquid may also be used as a pore-generating agent (i.e., as the solvent evaporates, it leaves voids, or pores), or the liquid may have additional functionality.

[0086] When making component A, the order of mixing can be important to retain solubility and activity of the component. For example, in an embodiment containing CQ and BPO in a PEG and ethyl acetate mixture, the ethyl acetate should be mixed with the CQ and BPO before the PEG is added. It is also beneficial to obtain homogeneity in component A to obtain a good polymer cure.

[0087] In a second embodiment, Component A contains a chemical radical generating component but no light radical generating component.

Amine Accelerator—Component B

[0088] In a first embodiment, Component B comprises a light accelerator component (or co-catalyst) and a reducing agent. Exposure of the photoinitiator to light generates a triplet state which reacts with the light accelerator co-catalyst component to form an active species that initiates polymerization. Preferred co-catalysts are amines, and more particularly the aromatic amines. Examples of aromatic amine accelerators include: N-alkyl substituted alkylamino benzoates, such as 4-ethyl-dimethyl amino benzoate (4-EDMAB); N-alkyl benzylamines such as N,N-dimethyl-benzylamine and N-isopropylbenzylamine; dibenzyl amine; 4-tolyldiethanolamine; and N-benzylethanolamine. Additionally, other suitable amine accelerators include N-alkyldiethanolamines such as N-methyldiethanolamine; triethanolamine; and triethylamine. One particularly preferred aromatic amine is 4-EDMAB.

[0089] The reducing agent, which is also called a chemical accelerator, is also in component B. A desirable reducing agent is one that is sufficiently reducing in nature to readily react with the preferred oxidizing agent, but not excessively reducing in nature such that it may reduce other components with which it may be combined during storage. Reduction of the resin with an inappropriate reducing agent could result in an unstable system that would prematurely polymerize and subsequently provide a limited shelf life.

[0090] A reducing agent has one or more functional groups for activation of the oxidizing agent. Preferably, such functional group(s) is selected from amines, mercaptans, or mixtures thereof. If more than one functional group is present, they may be part of the same compound or provided by different compounds. A preferred reducing agent is a

tertiary aromatic amine (e.g., N,N-dimethyl-p-toluidine (DMPT) or N,N-bis(2-hydroxyethyl)-p-toluidine (DHEPT)). Examples of such tertiary amines are well known in the art and are disclosed, for example, in WO 97/35916 and U.S. Pat. No. 6,624,211. Another preferred reducing agent is a mercaptan, which can include aromatic and/or aliphatic groups, and optionally polymerizable groups. Preferred mercaptans have a molecular weight greater than about 200 as these mercaptans have less intense odor. Other reducing agents, such as sulfinic acids, formic acid, ascorbic acid, hydrazines, some alcohols, and salts thereof, can also be used herein to initiate free radical polymerization.

[0091] If two or more reducing agents are used, they are preferably chosen such that at least one has a faster rate of activation than the other(s). That is, one causes a faster rate of initiation of the curing of the curable admixture than the other(s).

[0092] Electrochemical oxidation potentials of reducing agents and reduction potentials of oxidizing agents are useful tools for predicting the effectiveness of a suitable redox couple. For example, the reduction potential of the oxidant (i.e., oxidizing agent) benzoyl peroxide is approximately −0.16 volts vs. a saturated calomel electrode (SCE). Similarly, the oxidation potential (vs. SCE) for a series of amines has been previously established as follows: (e.g., N,N-dimethyl-p-toluidine ((DMPT), 0.61 volt), dihydroxyethyl-p-toluidine ((DHEPT), 0.76 volt), 4-t-butyl dimethylaniline ((t-BDMA), 0.77 volt), 4-dimethylaminophenethanol ((DMAPE), 0.78 volt), triethylamine ((TEA, 0.88 volt), 3-dimethylaminobenzoic acid ((3-DMAB) 0.93 volt), 4-dimethylarinobenzoic acid ((4-DMAB, 1.07 volts), ethyl p-dimethylaminobenzoate ((EDMAB), 1.07 volts), 2-ethylhexyl p-dimethylaminobenzoate ((EHDMAB), 1.09 volts) and 4-dimethylaminobenzoate ((DMABA), 1.15 volts). The ease of oxidation (and subsequent reactivity) increases as the magnitude of the oxidation decreases. Suitable amine reducing agents in combination with benzoyl peroxide generally include aromatic amines with reduction potentials less than about 1.00 volt vs. SCE. Less effective oxidants than benzoyl peroxide such as lauroyl peroxide (reduction potential=−0.60 volt) are poorer oxidizing agents and subsequently react more slowly with aromatic amine reducing agents. Suitable aromatic amines for lauroyl peroxide will generally include those having reduction potentials less than about 0.80 volt vs. SCE.

[0093] A preferred reducing agent is N,N-dimethyl-p-toluidine (DMT, also known as DMPT). When DMT is used, its percentage is preferably kept low to reduce heating of the sample that occurs during curing. It is preferred to keep the temperature below about 50° C. for the entire mixing process. In one particular exemplary embodiment, component B comprises 4-EDMAB and DMT in a ratio between 2:1 and 1:2.

[0094] In one embodiment, it is contemplated that a single agent (i.e., DMT) can be both the reducing agent and light accelerator of component B. This molecule must both have a suitable oxidation potential with the oxidizing agent and interact with the triplet state of the photoinitiator. In this embodiment, no other agent is required in component B.

[0095] It is also contemplated that instead of an oxidizing agent in component A and reducing agent in component B, component A will contain a reducing agent and component B will contain the oxidizing agent. For this embodiment, the selection of the redox couple must be done with care so as not to provide a reducing agent that can act as an accelerator or otherwise react with the photoinitiator before the crosslinking is initiated by mixing the components.

[0096] In a second embodiment, the present invention comprises an initiator system having only a chemical curing component. This initiator system is also divided into two parts, the first part (component A) comprising the chemical initiator and the second part (component B) comprises the chemical accelerator as discussed above.

[0097] Additional Initiators

[0098] Other initiators may also be added to the formulations of the present invention. Such initiators include additional photoinitiators or redox initiators. They also include thermal initiators, including peroxydicarbonate, persulfate (e.g., potassium persulfate or ammonium persulfate). Thermally activated initiators, alone or in combination with other type of initiators, are most useful where light can not reach (e.g., deep within the curable admixture). Additionally, multifunctional initiators may be used. These initiators may be added into component A or component B such that the initiator will not react with the other ingredients in component A or B before the component is mixed with the monomer, polymer, or other component.

Fillers

[0099] The curable admixture and/or cured composite of the present invention may contain the following optional fillers. These fillers, such as a bone substitutes may be incorporated into the polymer of the present invention. The filler, such as a bone substitute bone substituted is added when increased strength and/or slow resorption is required. The ratio of the bone substitute to crosslinkable prepolymer in the curable admixture may be a wide range of values. Preferably, the ratio is from 1:20 to 20:1; more preferably from 1:4 to 1:1; most preferably from about at about 1:2 to 1:1. The bone substitute can be any bone graft material known to one skilled in the art, preferably a ceramic or a polymer. Examples include Bioplant® HTR®, HA, TCP, and combinations thereof. It can be organic or synthetic or a combination thereof. Organic bone substitutes include autograft, allograft, xenograft or combinations thereof. Cadaver-derived materials and bovine-derived materials are non-limiting examples of allografts. Bovine-derived materials (e.g., Osteograft® N-300 and Osteograft® N-700) are non-limiting examples of xenografts. Synthetic bone substitutes are also known as alloplasts. Non-limiting examples of the alloplast include calcium phosphate and calcium sulfate ceramics and polymeric bone graft materials. In one embodiment, the bone substitute comprises an alloplast, more preferably a polymeric alloplast. The bone substitute may also be a polymer-ceramic hybrid, which is combination of a polymer material and a ceramic material mixed or combined to provide preferable properties of hardness, porosity, and resorbability.

Acrylic polymers (BIOPLANT® HTR®)

[0100] In one embodiment, the polymeric alloplast is preferably a plurality of micron-sized particles (preferably with a diameter from about 250 to 900 microns), each particle comprising a core layer comprised of a first poly-

meric material and a coating generally surrounding the core layer. The coating comprises a second polymeric material which is hydrophilic and has a composition different from the composition of the first polymeric material. Both polymeric materials in the polymeric alloplast are biocompatible. The first polymeric material is preferably an acrylic polymer and more preferably poly(methyl methacrylate) (PMMA). The PMMA may further include a plasticizer, if desired. The second polymeric material is preferably a polymeric hydroxyethyl methacrylate (PHEMA). Preferred polymeric particles are disclosed in the '485 patent, the specification of which is hereby incorporated by reference in its entirety.

[0101] In a more preferred embodiment, the bone substitute is a plurality of calcium hydroxide-treated polymeric micron-sized particles. The quantity of calcium hydroxide is effective to induce the growth of hard tissue in the pores and on the surface of the polymeric micron-sized particles when packed in a body cavity. Preferably, the calcium hydroxide forms a coating on both the outer and inner surfaces of the polymeric particles.

[0102] The micron-sized particles of the bone substitute may further optionally include a non-bonding agent, such as barium sulfate, to prevent the particles from bonding together. Barium sulfate is also a radio-opaque compound and may be included so as to render the curable admixture and the cured composite visible on an X-ray radiograph. The calcium hydroxide also assists in preventing the polymeric particles from bonding together.

[0103] Preferred procedures for producing the bone substitute component of the curable admixture of the present invention are set forth in the specification of the '158 patent. Preferably, calcium hydroxide is introduced into the pores of the micron-sized particles by soaking the particles in an aqueous solution of calcium hydroxide, then removing any excess solution from the particles and allowing the particles to dry. Preferred aqueous solutions of calcium hydroxide have a concentration in the range of from about 0.05 percent to about 1.0 percent calcium hydroxide by weight.

[0104] In a most preferred embodiment, the bone substitute is Bioplant® HTR,® available from Bioplant Inc. (Norwalk, Conn.), set forth in the '570 patent, which is hereby incorporated by reference in its entirety. The Bioplant® HTR® are microporous particles of calcified ($Ca(OH)_2$/calcium-carbonate) copolymer of PMMA and PHEMA, with the outer calcium layer interfacing with bone forming calcium carbonate-apatite. The outer diameter of the particles is about 750 μm; the inner diameter is about 600 pim and the pore opening diameter is about 350 μm. Bioplant® HTR® is strong (forces greater than 50,000 lb/in will not crush the Bioplant® HTR® particles), biocompatible and negatively charged (−10 mV) to promote cellular attraction and resist infection. In another embodiment, a smaller particle size Bioplant® HTR® is used, having an outer diameter of 200-400 μm. This smaller diameter Bioplant® HTR® could be more beneficial for injectable formulations where an ability to flow through a syringe is important.

[0105] Bioplant® HTR® is added to the composition of the present invention from 0-60% w/w. In one preferred embodiment, 30-50% Bioplant® HTR® will be added to the composition. This relatively large amount of Bioplant® HTR® provides the composition with a surface having a preferred surface composition for promoting new bone growth. In another embodiment, 20-30% Bioplant® HTR® is added to the composition.

[0106] *Hydroxyapatite (HA) and Tricalcium Phosphate (TCP)*

[0107] In one embodiment, the polymeric alloplast is preferably a hydroxyapatite (HA) filler. Hydroxyapatite, ($Ca_{10}(PO_4)_6(OH)_2$) is one of the most biocompatible materials with bones; it is naturally found in bone mineral and in the matrix of teeth and provides rigidity to bones and teeth. When a HA-containing material is used as a filler in the present invention, the modulus will be significantly increase.

[0108] A non-limiting list of HA bone substitute, or filler compounds that may be used in the present invention include: Pro Osteon® (Interpore Cross International, Inc., Irvine, Calif.) comprising monolithic ceramic granules, which are made using coralline calcium carbonate fully or partially converted to HA by a hydrothermal reaction, see D. M. Roy and S. K. Linnehan, *Nature,* 247, 220-222 (1974); R. Holmes, V. Mooney, R. Bucholz and A. Tencer, *Clin. Orthop. Rel. Res.,* 188, 252-262 (1984); and W. R. Walsh, et al., *J. Orthop. Res.,* 21, 4, 655-661 (2003). VITOSS®V (Orthovita, Malvern, Pa.) is provided as monolithic ceramic granules. Norian SRS® (Synthes-Stratec, affiliates across Europe and Latin America) and Alpha-BSM® (ETEX Corp., Cambridge, Mass.) are provided as an injectable pastes. ApaPore® and Pore-SI (ApaTech, London, England) are currently under development and comprise monolithic ceramic granules.

[0109] In one embodiment, the filler is preferably a material based upon HA, including the resorbable carbonated apatite. One particularly preferred HA, is a porous calcium phosphate material which is a porous hydroxyapatite and is more integrable, absorbable and more osteoconductive than dense hydroxyapatite. Porous HA can be made by the methods described in EP1411035, herein incorporated by reference. The aporosity can be controlled both as a ratio of the volume of material to the volume of air and as the porosity and pore size distribution.

[0110] Additionally, recent studies have elucidated the detrimental and beneficial effects of minor amounts of impurities and some dopants. Parts per million levels of lead, arsenic, and the like, if incorporated into hydroxyapatite, may lead to inhibition of osteoconduction. It is therefore preferable to use HA substantially free from these impurities. On the other hand, carbonated apatite exhibits faster bioresorption than pure HA, if desired, and 1-3 wt % silicon additions to HA have shown a two-fold increase in the rate of osteoconduction over pure HA, see N. Patel, et al., *J. Mater. Sci: Mater. Med.,* 13, 1199-206 (2002); and A. E. Portera, et al., *Biomaterials,* 24, 4609-4620 (2002). Silicon-doped HA such as the doped HA being developed at ApaTech and may be used as a filler in the present invention.

[0111] The HA is added to the composition of the present invention from 0-60% w/w. In one preferred embodiment, 20-30% HA is added to the composition.

[0112] In one embodiment, the filler is preferably a calcium phosphate material based upon HA, including alpha (α-TCP) or beta-tricalcium phosphate ($Ca_3(PO_4)_2$, α-TCP), which is a close synthetic equivalent to the composition of human bone mineral and has favorable resorption characteristics.

[0113] α-TCP has a high resorbability when the material is implanted in a bone defect and is sold as Biosorb®. Other calcium phosphates including biphasic calcium phosphate or BCP (an intimate mixture of HA and α-TCP) and unsintered apatite (AP) may also be used as bone substitutes in the present invention.

[0114] In another embodiment, the TCP material may be a TCP having a particularly small crystal size and/or particle size. This TCP (i.e., α- and/or β-TCP) is formed into high surface area powders, coatings, porous bodies, and dense articles by a wet chemical approach and transformed into TCP, for example by a calcination step such as that described in U.S. Pat. Pub. 2005/0031704, herein incorporated by reference. This TCP material, generally having an average TCP crystal size of about 250 nm or less and an average particle size of about 5 μm or less, has greater reliability and better mechanical properties as compared to conventional TCP having a coarser microstructure and is therefore one particularly preferred embodiment of the present invention.

[0115] Calcium

[0116] $Ca(OH)_2$, or $CaCO_3$ provides a good source of calcium for bone formation, it also provides a polymer surface that promotes bone growth. Additionally, the calcium will neutralize the pH of the polymer. This is particularly relevant when mSA is included in the formulation since this acid will alter the pH upon degradation. Non-limiting examples of compounds providing calcium including $Ca(OH)_2$, or $CaCO_3$, demineralized bone powder or particles, coral powder, calcium phosphate particles, α-tricalcium phosphate, octacalcium phosphate, calcium carbonate, and calcium sulfate. Preferably, such calcium compounds can neutralize the acid generated during the degradation of a biodegradable polymer and maintain a physiological pH value suitable for bone formation. It is preferably alkaline in nature so that it can neutralize the acid generated in the biodegradation process and help to maintain a physiological pH value.

[0117] Linear Polymers

[0118] Additional fillers such as a linear polyamide (PA), polyglycolic acid (PGA), polylactide (PLA), or a PGA/PLA copolymer can be added, for example, to reduce or eliminate shrinkage. For example, 1-25% of a linear PA may be used in a composition having 80% MCPP and 20% MSA. Greater amounts are generally not indicated due to a potential reduction in the consistency of the composition.

[0119] Other linear polymers are copolymers such as poly(CPH-SA) and poly(CPP-SA). These non-reactive polyanhydride copolymers may be added as an additional filler.

Additional Agents

[0120] One or more additional agents may also be added to the composition, dependant upon the intended use.

[0121] Inhibitors

[0122] Inhibitors may also be added to the formulation. Inhibitors can be used to prolong the shelf life of the individual components before curing the polymer system. A non-limiting list of inhibitors that may be added to the polymeric compositions of the present invention include phenols such as hydroquinone, mono methyl hydroquinone, and 2,6-bitertbutyl-4-methyl phenol; vitamin E; 4-tert butyl catechal; and aliphatic and aromatic amines such as phenylenediamines.

[0123] Excipients

[0124] One or more excipients may be incorporated into the compositions of the present invention.

[0125] Steric acid is a preferred excipient. Steric acid is non-reactive and acts as a diluent. It can be used to increase hydrophobicity, reduce strength, and increase consistency of the polymer formulation.

[0126] Ethyl acetate is another excipient that may be used to aid in the salvation and mixing as well as to obtain a viscosity useful for working with the polymerizable material.

[0127] Porosity Forming Agents

[0128] One or more substances that promote pore formation may be incorporated into the composition of the present invention; preferably in the curable composite.

[0129] Non-limiting examples of such substances include: particles of inorganic salts such as NaCl, $CaCl_2$, porous gelatin, carbohydrate (e.g., monosaccharide), oligosaccharide (e.g., lactose), polysaccharide (e.g., a polyglucoside such as dextran), gelatin derivative containing polymerizable side groups, porous polymeric particles, waxes, such as paraffin, bees wax, and carnaba wax, and wax-like substances, such as low melting or high melting low density polyethylene (LDPE), and petroleum jelly. Other useful materials include hydrophilic materials such as PEG, alginate, bone wax (fatty acid dimers), fatty acid esters such as mono-, di-, and tri-glycerides, cholesterol and cholesterol esters, and naphthalene. In addition, synthetic or biological polymeric materials such as proteins can be used.

[0130] The size or size distribution of the porosity forming agent particles used in the invention can vary according to the specific need. Preferably the particle size is less than about 5000 μm, more preferably between about 500 and about 5000 μm, even more preferably between about 25 and about 500 μm, and most desirably between about 100 and 250 μm.

[0131] Bone Promoting Agents

[0132] One or more substances that promote and/or induce bone formation may be incorporated into the compositions of the present invention. The bone promoting agent can include, for example, proteins originating from various animals including humans, microorganisms and plants, as well as those produced by chemical synthesis and using genetic engineering techniques. Such agents include, but are not limited to, biologically active substances such as growth factors such as, bFGF (basic fibroblast growth factor), acidic fibroblast growth factor (aFGF) EGF (epidermal growth factor), PDGF (platelet-derived growth factor), IGF (insulin-like growth factor), the TGF-β superfamily (including TGF-β s, activins, inhibins, growth and differentiation factors (GDFs), and bone morphogenetic proteins (BMPs)), cytokines, such as various interferons, including interferon-α, -β, and γ, and interleukin-2 and -3; hormones, such as, insulin, growth hormone-releasing factor and calcitonin; non-peptide hormones; antibiotics; chemical agents such as chemical mimetics of growth factors or growth factor recep-

tors, and gene and DNA constructs, including cDNA constructs and genomic constructs. In a preferred embodiment, the agents include those factors, proteinaceous or otherwise, which are found to play a role in the induction or conduction of growth of bone, ligaments, cartilage or other tissues associated with bone or joints, such as for example, BMP and bFGF. The present invention also encompasses the use of autologous or allogeneic cells encapsulated within the composition. The autologous cells may be those naturally occurring in the donor or cells that have been recombinantly modified to contain nucleic acid encoding desired protein products.

[0133] Non-limiting examples of suitable bone promoting materials include growth factors such as BMP (Sulzer Orthopedics), BMP-2 (Medtronic/Sofamor Danek), bFGF (Orquest/Anika Therapeutics), Epogen (Amgen), granulocyte colony-stimulating factor (G-CSF) (Amgen), Interleukin growth factor (IGF)-1 (Celtrix Pharmaceuticals), osteogenic protein (OP)-1 (Creative BioMolecules/Stryker Biotec), platelet-derived growth factor (PDGF) (Chiron), stem cell proliferation factor (SCPF) (University of Florida/Advanced Tissue Sciences), recombinant human interleukin (rhIL) (Genetics Institute), transforming growth factor beta (TGFβ) (Collagen Corporation/Zimmer Integra Life Sciences), and TGFβ-3 (OSI Pharmaceuticals). Bone formation may be reduced from several months to several weeks. In orthopedic and dental applications, bone regenerating molecules, seeding cells, and/or tissue can be incorporated into the compositions. For example bone morphogenic proteins such as those described in U.S. Pat. No. 5,011,691, the disclosure of which is incorporated herein by reference, can be used in these applications.

[0134] In one embodiment, the addition of a TGF-β superfamily member is particularly preferred. These proteins are expressed during bone and joint formation and have been implicated as endogenous regulators of skeletal development. They are also able to induce ectopic bone and cartilage formation and play a role in joint and cartilage development (Storm E E, Kingsley D M. *Dev Biol.* 1999 May 1;209(1): 1-27; Shimaoka et al., *J Biomed Mater Res A.* 200468(1):168-76; Lee et al., *J Periodontol.* 2003 74(6):865-72). The BMP proteins that may be used include, but are not limited to BMP-1 or a protein from one of the three subfamilies. BMP-2 (and the recombinant form rhBMP2) and BMP-4 have 80% amino acid sequence homology. BMP-5, -6, and -7 have 78% % amino acid sequence homology. BMP-3 is in a subfamily of its own. Normal bone contains approximately 0.002 mg BMP/kg bone. For BMP addition to induce bone growth at an osseous defect, 3 to 3.5 mg BMP has been found to be sufficient, although this number may vary depending upon the size of the defect and the length of time it will take for the BMP to release. Additional carriers for the BMP may be added, and include, for example, inorganic salts such as a calcium phosphate or CaO4S. (Rengachary, S S., *Neurosurg. Focus,* 13(6), 2 (2002)). Particular GDFs useful in the present invention include, but are not limited to GDF-1; GDF-3 (also known asVgr-2); the subgroup of related factors: GDF-5, GDF-6, and GDF-7; GDF-8 and highly related GDF-11; GDF-9 and -9B; GDF-10; and GDF-15 (also known as prostate-derived factor and placental bone morphogenetic protein).

[0135] It is important for the bone promoting agent to remain active through the polymerization process. For example, many enzymes, cytokines, etc. are sensitive to the radiation used to cure polymers during photopolymerization. The method provided in Baroli et al., *J. Pharmaceutical Sci.* 92:6 1186-1195 (2003) can be used to protect sensitive molecules from light-induced polymerization. This method provides protection using a gelatin-based wet granulation. This technique may be used to protect the bone promoting agent incorporated into the polymer composition.

[0136] Therapeutic Agents

[0137] One or more preventive or therapeutic active agents and salts or esters thereof may be incorporated into the compositions of the present invention, including but not limited to:

[0138] antipyretic analgesic anti-inflammatory agents, including non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, aspirin, diclofenac sodium, ketoprofen, ibuprofen, mefenamic acid, azulene, phenacetin, isopropylantipyrin, acetaminophen, benzydamine hydrochloride, phenylbutazone, flufenamic acid, mefenamic acid, sodium salicylate, choline salicylate, sasapyrine, clofezone or etodolac; and steroidal drugs such as dexamethasone, dexamethasone sodium sulfate, hydrocortisone, or prednisolone;

[0139] antibacterial and antifungal agents such as penicillin, ampicillin, amoxicillin, cephalexin, erythromycin ethylsuccinate, bacampicillin hydrochloride, minocycline hydrochloride, chloramphericol, tetracycline, erythromycin, fluconazole, itraconazole, ketoconazole, miconazole, terbinafine; nlidixic acid, piromidic acid, pipemidic acid trihydrate, enoxacin, cinoxacin, ofloxacin, norfloxacin, ciprofloxacin hydrochloride, sulfamethoxazole, or trimethoprim;

[0140] anti-viral agents such as trisodium phosphonoformate, didanosine, dideoxycytidine, azido-deoxythymidine, didehydro-deoxythymidine, adefovir dipivoxil, abacavir, amprenavir, delavirdine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir or stavudine;

[0141] high potency analgesics such as codeine, dihydrocodeine, hydrocodone, morphine, dilandid, demoral, fentanyl, pentazocine, oxycodone, pentazocine or propoxyphene; and

[0142] salicylates which can be used to treat heart conditions or as an anti-inflammatory.

[0143] The agents can be incorporated in the composition of the invention directly, or can be incorporated in microparticles which are then incorporated in the composition. Incorporating the agents in microparticles can be advantageous for those agents, which are reactive with one or more of the components of the composition.

[0144] The method described in Baroli et al., *J. Pharmaceutical Sci.* 92:6 1186-1195 (2003) can be used to protect sensitive therapeutic agents from light-induced polymerization when incorporated in the polymer composition.

[0145] Diagnostic Agents

[0146] One or more diagnostic agents may be incorporated into the compositions of the present invention. Diagnostic/

imaging agents can be used which allow one to monitor bone repair following implantation of the compositions in a patient. Suitable agents include commercially available agents used in positron emission tomography (PET), computer assisted tomography (CAT), single photon emission computerized tomography, X-ray, fluoroscopy, and magnetic resonance imaging (MRI).

[0147] Examples of suitable agents useful in MRI include the gadolinium chelates currently available, such as diethylene triamine pentaacetic acid (DTPA) and gadopentotate dimeglumine, as well as iron, magnesium, manganese, copper and chromium gadolinium chelates.

[0148] Examples of suitable agents useful for CAT and X-rays include iodine based materials, such as ionic monomers typified by diatrizoate and iothalamate, non-ionic monomers such as iopamidol, isohexol, and ioversol, non-ionic dimers, such as iotrol and iodixanol, and ionic dimers, for example, ioxagalte.

[0149] These agents can be detected using standard techniques available in the art and commercially available equipment.

Crosslinking the Curable Admixture to Form the Cured Composite

[0150] The curable admixture is crosslinked through the use of component A and B and, when photoinitiation is used, light to form the cured composite. The components are mixed thoroughly with the polymer or prepolymer(s). A ball mixer may be used to improve the consistency of mixing.

[0151] It is important to keep component A separated from component B before initiating polymerization so that the materials within the two components do not react or cure before the polymerization reaction is started. In some instances, it is similarly important to keep component A separated from the polymers or polymerizable material before use since the photochemical initiator can initiate at least some polymerization even without the accelerator component.

[0152] The concentration of the initiator(s) used is dependant on a number of factors. Non-limiting examples of such factors include the type of the initiator, whether the initiator is used alone or in combination with other initiators, the desirable rate of curing, and how the material is applied. The concentration of each initiator is between about 0.05% (w/w) to about 5% (w/w) of the crosslinkable prepolymer. Preferably, the concentration is less than 1% (w/w) of the crosslinkable prepolymer; more preferably between 0.01 and 0.1% (w/w). In one embodiment, 20 μl of component A (0.5/ml total initiators) and 20 μl of component B (0.4 g/ml total initiators) are added per gram of polymer. In another embodiment, 40 R1 of each component is added per gram of polymer to effect a stronger polymer.

[0153] It is preferred to utilize a particular sequence of adding the initiator components A and B, since mixing in any other order could drastically reduce the amount or homogeneity of the polymerization reaction. In one illustrative embodiment, component A is mixed with the polymer or prepolymer until evenly dispersed. Next, component B is mixed into the composition. If the mixing of component B was rapid, the mixture should be allowed to stand for about 10-30 seconds (with optional occasional mixing). The viscosity of the mixture should noticeably increase. At this point, it is possible to transfer into a mold or inject into a space in which the polymerization should occur. Light is then directed onto the sample for 0.5, 1, 2, 3, or more minutes to complete curing. The light may, for example, be a UV, white, or blue light. A dental blue light (e.g., a Demitron or a 3M light) may be used. Most of the photo-initiated curing should occur within one minute, however, longer exposure to the light is also acceptable.

[0154] Samples of up to 1.5 cm have been cured in this manner. It is possible to cure thicker samples that are less opaque or where the chemical curing provides substantially more of the cure in the sample section farther from the light source. The size and shape of the sample is a factor in the curing of the polymer; thicker samples will take longer to cure. Additionally, larger samples may not receive the same exposure to the light source across the sample surface due to the size of the source and variations in light intensity. Since many light sources have a Gaussian profile, it may be advisable to move either the sample or the light source across the sample surface during curing to effect an evenly cured composite.

[0155] In the embodiments of the present invention where only chemical curing is used, components A and B will contain the redox components but not the photocuring agents. In one such preferred embodiment, in which component A contains benzoyl peroxide and component B contains DMT, these can be combined to initiate curing in a molar ratio of approximately 1:1. The same initiator concentration as used for combined light and chemical curing may be used for chemical-only curing, and is preferably below 1%.

[0156] In one embodiment, the crosslinkable monomer or polymer and initiator B are combined prior to use. Initiator component B may contain a photo initiator and a redox agent, just a redox agent, or an agent that is effective as both a photo initiator and a redox agent. This mixture is mixed with initiator component A when the composite material is needed, forming a simple two-phase system. The material is then packed in the bone cavity or other area, and light is directed onto the mixture to initiate polymerization if applicable.

[0157] In another embodiment, the crosslinkable monomer or polymer and initiator Component A are combined prior to use. This mixture is mixed with initiator component B when the composite material is needed, forming a simple two-phase system. The material is then packed in the bone cavity or other area, and light is directed onto the mixture to initiate polymerization if applicable.

[0158] The crosslinkable bone substitute is subjected to electromagnetic radiation from a radiation source for a period sufficient to crosslink the bone substitute and form a crosslinked composite. Preferably, the crosslinkable bone substitute is applied in layer(s) of 1-10 mm, more preferably about 3-5 mm, and subjected to an electromagnetic radiation for about 30 to 300 seconds, preferably for about 50 to 100 seconds, and more preferably for about 60 seconds.

[0159] Typically, a minimum of 0.01 mW/cm^2 intensity is needed to induce polymerization. Maximum light intensity can range from 1 to 1000 mW/cm^2, depending upon the wavelength of radiation. Tissues can be exposed to higher

light intensities, for example, to longer wavelength visible light, which causes less tissue/cell damage than shortwave UV light. In dental applications, blue light is used at intensities of 100 to 400 mW/cm^2 clinically. When UV light is used in situ, it is preferred that the light intensity is kept below 20 mW/cm^2.

[0160] In another embodiment, when a thermally activated initiator is used, the crosslinkable bone substitute is subjected to a temperature suitable for activating the thermally activated initiators, preferably at a temperature from about 20 to 80° C., more preferably from about 30 to 60° C. Heat required to activate the thermal activator can be generated by various known means, including but not limited to infrared, water bath, oil bath, microwave, ultrasound, or mechanical means. For example, one can place the bone substitute in a crucible heated by a hot water bath.

[0161] In yet another embodiment, when a redox initiator system is used (alone or in combination with other type(s) of initiator(s)), the oxidizing agent of the redox initiator system is kept apart from the reducing agent of the redox initiator system until immediately before the curing process. For example, the oxidizing agent is mixed with some crosslinkable bone substitute in one container and the reducing agent is also mixed with some crosslinkable bone substitute in another container. The contents of the two containers are mixed with each other at which point substantial crosslinking is initiated.

[0162] In a most preferred embodiment, in order to shorten the duration of the radiation exposure and/or increase the thickness of the radiation crosslinkable layer, a redox initiator system is used in combination with a photoinitiator and/or thermal initiator. For example, the redox initiator system is activated first to partially crosslink the crosslinkable bone substitute. Such partially crosslinked bone substitute is then subjected to radiation and the photoinitiator and/or thermal initiator is activated to further crosslink the partially crosslinked admixture.

[0163] As used herein: "Electromagnetic radiation" refers to energy waves of the electromagnetic spectrum including, but not limited to, X-ray, ultraviolet, visible, infrared, far infrared, microwave, radio-frequency, sound and ultrasound waves. "X-ray" refers to energy waves having a wavelength of 1×10^{-9} to 1×10^{-6} cm. "Ultraviolet light" refers to energy waves having a wavelength of at least approximately 1.0×10^{-6} cm but less than 4.0×10^{-5} cm. "Visible light" refers to energy waves having a wavelength of at least approximately 4.0×10^{-5} cm to about 7.0×10^{-5} cm. "Blue light" refers to energy waves having a wavelength of at least approximately 4.2×10^{-5} cm but less than 4.9×10^{-5} cm. "Red light" refers to energy waves having a wavelength of at least approximately 6.5×10^{-5} cm but less than 7.0×10^{-5} cm. "Infrared" refers to energy waves having a wavelength of at least approximately 7.0×10^{-5} cm.

[0164] Audible sound waves are in frequency ranges from 20 to 20,000 Hz. Infrasonic waves are in frequency ranges below 20 Hz. Ultrasonic waves are in frequency ranges above 20,000 Hz. "Radiation source" as used herein refers to a source of electromagnetic radiation. Examples include, but are not limited to, lamps, the sun, blue lamps, and ultraviolet lamps.

[0165] The consistence of the compositions of the present invention before curing can be varied, depending upon the intended use. For example, a flowable composition is used when delivery via a syringe is desired; a putty is useful where the composition is to be placed in an exposed bone socket; and a solid may be used (alone in combination with a flowable or putty-like composition) when the final shape is known.

[0166] The curable admixture may be used in place of bone, such as in a tooth socket or other bony void (i.e., the spine), or may be placed in place of soft tissue, such as the area surrounding a tooth socket.

Property of the Curable Admixture and the Cured Composite

[0167] Strength

[0168] It is preferred that the strength of the cured composite be from about 5 to 300 N/m^2; more preferably from about 20 to 200 N/m^2; and most desirably from about 50 to 200 N/m^2. The strength of the cured composite depends on a number of factors, such as the ratio between the bone substitute and crosslinkable prepolymer, and the crosslinking density of the cured composite.

[0169] In a preferred embodiment, that the cured composite has a compressive strength of at least 10 MPa. In one embodiment, the compressive strength is 20 to 30 MPa.

[0170] Porosity

[0171] High porosity is an important characteristic of the present invention. The bone substitute is porous to allow bone growth within the scaffold of the bone substitute, including the interstitial region between the particles when packed into an implant.

[0172] Hydrophobicity/Hydrophilicity

[0173] The hydrophobicity/hydrophilicity of the curable admixture and the cured composite should be carefully controlled. Preferably, the curable admixture and cured composite are sufficiently hydrophilic that cells adhere well to them. The hydrophobicity/hydrophilicity depends on a number of factors such as the hydrophobicity/hydrophilicity of the bone substitute and/or the crosslinkable prepolymer. For example, when the bone substitute is a PMMA/PHEMA based polymer particle, the ratio of PMMA (less hydrophilic) and PHEMA (more hydrophilic) affects the hydrophobicity/hydrophilicity. As another example, if the crosslinkable prepolymer is a polyanhydride instead of a polyethylene glycol, the curable admixture and the cured composite are more hydrophobic.

[0174] Viscosity

[0175] The viscosity of the curable admixture can vary widely. It depends on a number of factors such as the molecular weight of the ingredients in the curable admixture, and the temperature of the curable admixture. Typically, when the temperature is low, the curable admixture is more viscous; and, when the average molecular weight of the ingredients is high, it becomes more viscous. Different applications of the curable admixture also require different viscosities. For example, to be injectable, the admixture must be a free flowing liquid and, in other applications, it must be a moldable paste-like putty.

[0176] The viscosity of the curable admixture may be adjusted by formulating the crosslinkable prepolymer with a suitable amount of one or more biocompatible unsaturated

functional monomers such as the ones described in U.S. Pat. Pub. 2003/114552 which are incorporated herein by reference.

[0177] Biodegtadation/Bioresorption Duration

[0178] The time needed for biodegradation/bioresorption of the curable admixture and/or the cured composite can be varied widely, from days to years; preferably from weeks to months. The suitable biodegradation/bioresorption duration depends on a number of factors such as the speed of osteointegration, whether the compositions are functional and/or load-bearing, and/or the desirable rate of drug release. For example, osteointegration in an elderly woman is typically much slower than that in a 20 year old man. When osteointegration is slow, a composition having a long biodegradation/bioresorption time should be used. An immediately functional dental implant is load-bearing and must remain strong during osteointegration, so a long biodegradation/bioresorption composition is more suitable for application around such dental implant. If a therapeutic agent is intended to be released over a long period of time, a long biodegradation/bioresorption composition is more suitable.

[0179] Depending on the specific application, the time required can be manipulated based on a number of factors, e.g., the ratio of the bone substitute and the crosslinkable prepolymer. When the crosslinkable prepolymer contains more than one type of monomer, the ratio of the monomers also plays a crucial role in the degradation/resorption time. For example, when the crosslinkable prepolymer contains a mixture of dimethacrylated anhydrides of sebacic acid and 1,3-bis(p-carboxyphenxy)-propane, increasing the proportion of dimethacrylated anhydride of sebacic acid decreases the degradation/resorption time. Further, when the bone substitute is PMMA/PHEMA-based (known to be very slowly degradable), increasing the proportion of the bone substitute increases degradation time.

[0180] The degradation time is a function of the pH. For example, anhydrides are typically more susceptible to degradation in alkaline condition than in acidic condition.

[0181] The degradation time is a function of the hydrophobicity/hydrophilicity of the components. For example, when 1,3-bis(p-carboxyphenxy)-hexane (more hydrophobic) is replaced by 1,3-bis(p-carboxyphenxy)-propane (less hydrophobic), degradation time decreases.

[0182] The degradation time is also a function of geometrical shape, thickness, etc.

[0183] Where rapid degradation is sought, at least about 15% (w/w), preferably about 50% (w/w), of the cured composite degrades or resorbs in about 5-10 weeks, preferably in about 6-8 weeks.

[0184] On the other hand, for slow degradation at least about 15% (w/w), preferably about 50% (w/w), of the cured composite degrades or resorbs in about 6-12 months, preferably in about 9 months.

Application of the Curable Admixture and the Cured Composite

[0185] Dental

[0186] The curable admixture and cured composite of the present invention can be used to fill extraction sockets; prevent or repair bone loss due to tooth extraction; repair jaw bone fractures; fill bone voids due to disease and trauma; stabilize an implant placed into an extraction socket and one placed into an edentulous jawbone to provide immediate function (e.g., chewing); provide ridge (of bone) augmentation; repair periodontal bone lesions; and provide esthetic gingiva reshaping and plumping. When the curable admixture and/or the cured composite is used for dental implant applications, preferably, the dental implant is partially or fully embedded into the cured composite according one of the following two methods:

[0187] Method (1):

[0188] Planting a dental implant into a bone and/or bone void;

[0189] at least partially embedding the dental implant by applying a curable admixture around the dental implant;

[0190] curing the curable admixture to form a cured composite; and

[0191] repeating steps (b) and (c) if necessary.

[0192] Method (2)

[0193] At least partially filling a bone void by applying the curable admixture;

[0194] curing the curable admixture to form a cured composite;

[0195] repeating steps (a) and (b) if necessary;

[0196] planting a dental implant into the bone by at least partially embedding the dental implant into the cured composite.

[0197] The curable admixture can be crosslinked by exposure to electromagnetic radiation and/or heat and applied using standard dental or surgical techniques. The curable admixture may be applied to the site where bone growth is desired and cured to form the cured composite and cured to form the cured composite. The curable admixture may also be pre-cast into a desired shape and size (e.g., rods, pins, screws, and plates) and cured to form the cured composite.

[0198] Orthopedic

[0199] The curable admixture and cured composite of the present invention can be used to repair bone fractures, fix vertebrae together, repair large bone loss (e.g., due to disease) and provide immediate function and support for load-bearing bones; to aid in esthetics (e.g., chin, cheek, etc.). The curable admixture can be applied using standard orthopedic or surgical techniques; e.g., it can be applied to a site where bone generation is desired and cured to form the cured composite. For example, the admixture can be applied into the intervertebral space. The curable admixture may also be pre-cast into a desired shape and size (e.g., rods, pins, screws, plates, and prosthetic devices such as for the spine, skull, chin and cheek) and cured to form the cured composite.

[0200] Drug Delivery

[0201] The curable admixture and cured composite of the present invention may be used to deliver therapeutic or diagnostic agents in vivo. Examples of drugs or agents which can be incorporated into such compositions include proteins, carbohydrates, nucleic acids, and inorganic and

organic biologically active molecules. Specific examples include enzymes, antibiotics, antineoplastic agents, local anesthetics, hormones such as growth hormones, angiogenic agents, antiangiogenic agents, antibodies, neurotransmitters, psychoactive drugs, drugs affecting reproductive organs, and oligonucleotides such as antisense oligonucleotides.

EXAMPLES

[0202] The following examples are intended to illustrate more specifically the embodiments of the invention. It will be understood that, while the invention as described therein is a specific embodiment, the description and the example are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to those skilled in the art to which the invention pertains.

Example 1

[0203] This example illustrates the invention with the first embodiment of the crosslinkable prepolymer.

[0204] Curable admixtures are formed by mixing two crosslinkable prepolymers: (1) dimethacrylated anhydride of sebacic acid and (2) dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane) with a bone substitute: (Bioplant® HTR®) as follows.

Formulation A

[0205]

Ingredient	Weight
dimethacrylated anhydride of sebacic acid	325 mg
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	175 mg
DL-camphoquinone	5 mg
N-phenylglycine	5 mg
Bioplant ® HTR ®	510 mg

[0206] The dimethacrylated anhydride of sebacic acid is formed by reacting sebacic acid with methacrylic anhydride by heating at reflux and the dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane is formed by reacting 1,3-bis(p-carboxyphenoxy) propane with methacrylic anhydride by heating at reflux. DL-camphoquinone is used as a photoinitiator. This material is designed to be significantly resorbed in about 6-9 weeks when cured.

Formulation B

[0207]

Ingredient	Weight
dimethacrylated anhydride of sebacic acid	175 mg
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	325 mg
DL-camphoquinone	5 mg
N-phenylglycine	5 mg
Bioplant ® HTR ®	510 mg

[0208] This material is designed to be significantly resorbed in about 9 months.

Example 2

[0209] This example illustrates the invention with the second embodiment of the crosslinkable prepolymer.

Formulation C

[0210]

Ingredient	Weight
dimethacrylated anhydride of sebacic acid	125 mg
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	125 mg
Poly(1,3-bis(p-carboxyphenoxy) propane:sebacic acid) (80:20)	250 mg
Irgacure 651 (Ciba-Geigy)	1 mg
Bioplant ® HTR ®	501 mg

[0211] Poly(1,3-bis(p-carboxyphenoxy) propane:sebacic acid) (80:20) ("Poly(CPP:SA) (80:20)") is a 80:20 (molar ratio) linear co-polymer of 1,3-bis(p-carboxyphenoxy) propane and sebacic acid. It is synthesized according to the procedure described in the Rosen et al. *Biomaterials,* 4, 131, (1983); Domb and Langer, *J. Polym. Sci.,* 23, 3375, (1987).

Example 3

[0212] This example illustrates the invention with the third embodiment of the crosslinkable prepolymer. The formulations are examples of a curable admixture formed by mixing (1) a crosslinkable prepolymer having at least two polymerizable terminal groups and a hydrophilic region with (2) bone substitute.

Formulation D

[0213]

Ingredient	Weight
polyester bis-methacrylate	254.6 mg
demineralized bone powder	256.2 mg
DL-camphoquinone	4.42 mg
N-phenylglycine	2.54 mg
Bioplant ® HTR ®	517.76 mg

[0214] The polyester bis-methacrylate is prepared according to the method described in Example 1 of WO01/74411.

Formulation E

[0215]

Ingredient	Weight
poly(D,L-lactide$_{50}$-co-ε-caprolactone)-hexanediol$_{20/1}$-methacrylate	250 mg
α-tricalcumphosphate	250 mg

-continued

Ingredient	Weight
DL-camphorquinone	1.2 mg
N-phenylglycine	1.1 mg
Bioplant ® HTR ®	502.3 mg

[0216] The poly(D,L-lactide$_{50}$-co-ε-caprolactone)-hexanediol$_{20/1}$-methacrylate is prepared according to the method described in WO 01/74411.

Example 4

[0217] The following experiment was conducted to study the bone ingrowth after extraction of molars and immediate fixation of an implant and placement of the curable admixture of the present invention. Formulation D of Example 3 was used.

[0218] Seven female sheep, ages 3 to 5 years, and thus having mature dentition, were used in the experiment. Two weeks prior to the extraction of teeth, the general health and dentition of the sheep were examined. If necessary, medication was used for de-vermification. Two days prior to the extraction, lateral and oblique pre-operation X-rays of the teeth to be removed were taken. One day prior to extraction, feeding was stopped and prophylactic AB (Excenel® RTU) and NSAID (Finadyne®) were administered. The next day (day 0) the P3 and P4 molars were extracted from both the left and right mandibles of the sheep. Preoperative medication of AB (Excenel® RTU) and Methylprednisolon (0.5 mg/kg, IM) was administered. The curable admixture in Example 3, Formulation D, was applied and cured in layers. The maximum thickness of each layer is about 5 mm. The light source was a standard dental 3M light in the visible light range. For each layer, the light was applied for 80 seconds.

[0219] In the left mandible, two titanium implants (Ankylos®), one normal and one modified with a square neck, were placed in one extraction socket. No implant was placed in the other socket. Bioplant® HTR® was mixed with Platelets Rich Plasma (PRP) and placed in the first socket around the implants as well as in the socket without implants. Bioplant® HTR® was then combined with the light curable polymer and placed in the first socket around the neck of the implants and in the occlusal part of the second socket without the implants. The strength of the mixture was from about 30 to about 40 N/m^2.

[0220] In the right mandible, two titanium implants (Ankylos®), one normal and one modified with a square neck, were placed in one extraction socket. No implant was placed in the other socket. Bioplant® HTR® was mixed with marrow bleeding and placed around the implants and in the socket without implants. Bioplant® HTR® was then combined with the light curable polymer and placed around the neck of the implants and in the occlusal part of the socket without the implants.

[0221] On days 1-3 AB (Excenel® RTU) (1 mg/kg) was administered. On day 30, 90 and 180 conventional and intra-oral X-rays were taken. On day 180, the sheep were euthanized and biopsies were performed for histological test.

Example 5

[0222] The lower anterior incisor of Patient A was falling out due to advanced gingival and bone disease. Pre-operative X-ray revealed that there was almost no bone around the tooth (98% gone, bone resorbed because of gem infection). Abscess and infection were observed. The tooth was about 99% mobile and had to be held in place with fingers. If a normal apicoectomy were conducted, the tooth would not have survived (i.e., it would have fallen out).

[0223] After debridement of the area around the tooth, the curable admixture, Formulation D, was applied around the lower portion of the tooth in layers. Each layer was about 5 mm thick. After the application of each layer, the material in that layer was hardened in situ with blue dental light (source: 3M® Light) for about 80 seconds. The next layer was applied immediately after the previous layer was hardened. After the desirable stability and thickness was reached and esthetic shape or gingiva was obtained, the surgical flap was repositioned and sutured closed. The tooth was immediately stable, functional, and free of significant micromovement following the surgery. Twenty days and 3 months after surgery, the area was X-rayed to reveal significant bone growth.

Example 6

[0224] The upper left central incisor of Patient B had a bone void of 98% due to the tooth extraction and the failed grafting of the socket area with Algipore® (General Medical, UK) graft material. Infection and graft failure resulted not only the loss of a portion of the Algipore® graft, but also the destruction of the entire buccal plate and the adjacent bone. The failed Algipore® was surrounded by infected soft tissue.

[0225] The failed Algipore® was first surgically removed. After debridement of the area, a large bone void was revealed. A metal implant was planted into the bone void with hand instrumentation and was stabilized by bone at the apex of the defect. There was only about 2 min stabilization bone at the apex. Next, the curable admixture made according to Example 3, Formulation D, was applied around the implant in layers of approximately 5 mm or less and cured (hardened) with standard dental light for about 80 seconds. After the first layer was hardened, the next layer was added and cured. More layers were added and cured until the desired thickness for stability and esthetics was reached. Next, the soft tissue around the implant was sutured. An immediate post-operative temporary jacket was added and placed in function (e.g., contact for chewing). The implant was immediately functional, stable, and free of significant micromovement. X-rays taken 28 days after the surgery and implantation show bone growth was observed around the metal implant. There was no infection.

Example 7

[0226] In addition to the synthesis method described in Example 1, methacrylated sebacic acids (MSA) and (1,3-bis(carboxyphenoxy))propyl dimethacrylate (CPPDM) were prepared according to the procedure described by Tarcha et al. *J. Polym. Sci, Part A, Polym. Chem.* (2001), 39, 4189. The MSA was synthesized by reacting sebacyl chloride and methacrylic acid at 0° C. in the presence of triethylamine and dichloromethane. The CPPDM was prepared by react-

ing methacrylocyl and 1,3-bis(p-caboxyphenoxy) propane (CPP) at 0° C. in the presence of triethylamine and dichloromethane.

Example 8

[0227] Samples Prepared

[0228] Nine samples were prepared as follows:

[0229] (1) 50 wt %: 50 wt % LC: HTR (where LC is 100 wt % MSA);

[0230] (2) 45 wt %: 45 wt % :10 wt % LC: HTR: sucrose (where LC is 100 wt % MSA);

[0231] (3) 50 wt %: 50 wt % LC: HTR (where LC is 50 wt % MSA and 50 wt % CPPDM);

[0232] (4) 75 wt %: 25 wt % LC: HTR (where LC is 100 wt % MSA);

[0233] (5) 75 wt %: 25 wt % LC: HTR (where LC is 90 wt % CPPDM and 10 wt % MSA);

[0234] (6) 90 wt %: 10 wt % LC: sucrose (where LC is 90 wt % CPPDM and 10 wt % MSA);

[0235] (7) 90 wt %: 10 wt % LC: HTR (where LC is 90 wt % CPPDM and 10 wt % MSA);

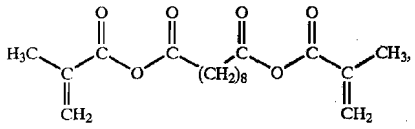
[0236] (8) 90 wt %: 5 wt %: 5 wt % LC:HTR:sucrose (where LC is 90 wt % CPPDM, and 10 wt % MSA); and

[0237] (9) 100 wt % LC (where LC 90 wt % CPPDM and 10 wt % MSA).

[0238] HTR is abbreviation for Bioplanto HTR,O available from Bioplant Inc. (Norwalk, Conn.).

[0239] LC is abbreviation for light curable material. In these 9 samples, LC is MSA, CPPDM, or combination thereof.

[0240] MSA is abbreviation for methacrylated sebacic acid:



[0241] synthesized according to the procedure described by Tarcha et al. *J. Polym. Sci, Part A, Polym. Chem.* (2001), 39, 4189.

[0242] CPPDM is abbreviation for (1,3-bis(carboxyphenoxy))propyl dimethacrylate:

[0243] synthesized according to the procedure described by Tarcha et al. *J. Polym. Sci, Part A, Polym. Chem.* (2001), 39, 4189.

Example 9

[0244] Photopolyermization

[0245] To photopolymerize the samples in Example 8, an initiating system with ethyl 4-dimethylaminobenzoate in conjunction with an equal amount of camphorquinone was used. The ethyl 4-dimethylaminobenzoate and camphorquinone were dissolved in ethanol and added to each of the nine samples of Example 8 at 0.5 wt % relative to the total solids content (LC/HTR/sucrose combined).

[0246] The mixture was packed into teflon molds containing 5 mm holes, placed between two glass slides and exposed to a 450 nm visible light source to produce 1 mm thick disks for in vitro degradation experiments (Example 10 below) or 110 mm thick cylinders for in vitro mechanical strength testing (Example 11 below). Such in vitro tests provide good initial assessment as to whether the material would be useful for orthopedic or dental applications. For example, (1) high compressive yield strength indicates that the material is suitable for immediate dental implant purposes, because such dental implants would be able to withstand the biting and/or chewing forces immediately; and (2) percentage of mass loss within a certain time period indicates how fast the material would resorb in vivo and provide a situs for bone/tissue growth.

Example 10

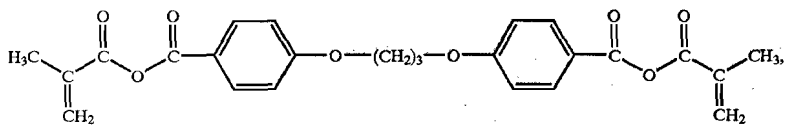
[0247] Degradation Experiments

[0248] The disks prepared in Example 9 (5 mm in diameter×1 mm in thickness) were placed in individual tubes. The tubes were filled with approximately 1.5 ml of phosphate buffered saline (adjusted to pH 7.4) and the tubes were placed in a shaker incubator thermostatted at 37° C.; the buffer was removed and replaced every 1-2 days. Samples were removed periodically, weighed wet, then dried and reweighed. This allowed for calculation of the equilibrium swelling values as well as the mass loss over time. Data was collected in triplicate.

Example 11

[0249] Mechanical Strength Tests

[0250] The cylinders prepared in Example 9 (5 mm in diameter×10 mm in height) were used for the mechanical strength tests. Unconstrained uniaxial compression test were used to evaluate the mechanical properties of the cylinders at room temperature. Standard method was used to calibrate a 500 N load cell before testing. Five specimens of the each sample were mounted on a mechanical analyzer with the



calibrated load cell. Specimens that broke at obvious flaws (e.g., water pocket or air pocket formation) were discarded. Strain was calculated from crosshead displacement. Stress was calculated from the load and cross-sectional area.

[0251] The ends of the samples were checked to make sure they are parallel to each other. Samples containing sucrose (i.e., Samples 2, 6, and 8) were soaked in de-ionized water overnight right before the testing date. All specimens were tested at 24° C. and ambient humidity.

load: the maximum compressive force applied to the specimen, under the conditions of testing, that produces a designated degree of failure.

Example 12

[0254] Results and Discussion

[0255] The results of the degradation experiment (Example 10) and mechanical strength tests are summarized below.

TABLE 1

Results of testing for LC/BioPlant HTR formulations.

Sample[1]	LC[2] (wt %)	HTR (wt %)	Sucrose (wt %)	Compressive yield strain (%)	Compressive yield strength (MPa)	Crushing Load (MPa)	Integrity lost (days)	Swelling wt % in water	% Mass loss (# days)
1	50[3]	50	0	—	12.59 (±2.441)	—	4	slight amount, 50 wt %	43 ± 2 (20)
2	45[3]	45	10	—	4.365 (±1.334)[6]	—	4	slight amount, 50 wt %	49 ± 3 (18)
3	50[4]	50	0	—	—	—	6	slight amount, 50 wt %	35 ± 2 (21)
4	75[3]	25	0	—	—	—	8	100 wt %	62 ± 4 (21)
5	75[5]	25	0	6.285 (±1.30)	18.81 (±3.107)	19.06 (±3.15)	11	50 wt %	45 ± 2 (44)
6	90[5]	0	10	5.186 (±0.4822)	9.295 (±1.249)[6]	22.44 (±4.908)	11	>200 wt %	56 ± 6 (44)
7	90[5]	10	0	6.484 (±0.3490)	23.19 (±1.612)	—	36	slight amount, 50 wt %	40 ± 4 (48)
8	90[5]	5	5	9.082 (±1.229)	21.79 (±2.834)[6]	22.92 (±2.584)	36	slight amount, 50 wt %	47 ± 2 (48)
9	100[5]	0	0	5.878 (±0.8676)	11.67 (±3.028)	14.36 (±4.121)	56	75 wt % after 36 days	40 ± 3 (36)

[1]Photopolymerization conditions: 0.5 wt % camphorquinone, 0.5 wt % ethyl 4-dimethylaminobenzoate, λ = 450 nm
[2]MSA = methacrylated sebacic acid, CPPDM = (1,3-bis(carboxyphenoxy))propyl dimethacrylate
[3]composition = 100 wt % MSA
[4]composition = 50 wt % MSA/50 wt % CPPDM
[5]composition = 10 wt % MSA/90 wt % CPPDM
[6]soaked in deionized water to remove sucrose prior to testing

[0252] The diameter of each sample was measured by a caliper to the nearest 0.01 mm at several points along its length. The minimum cross-sectional areas were calculated. The length of each specimen was measured to the nearest 0.01 mm. A concentric semi-circular mold was made to precisely mount the specimen at the center of the bottom anvil. Each specimen was mounted against the semi-circular mold between the surfaces of the anvils of the compression tool. The crosshead of the testing machine was adjusted until it just contacts the top of the compression tool plunger. The speed of the test was set at 1.3±0.3 mm/min. Loads and the corresponding compressive strain at appropriate intervals of strain were recorded to get the complete load-deformation curve. The maximum load carried by each specimen during the test (at the moment of rupture) was also recorded. If a specimen was relatively ductile, the speed was increased to 6 mmn/min after the yield point had been reached; and the machine was run at this speed until the specimen breaks. The end point of the test was when the specimen was crushed to failure.

[0253] The following properties were calculated: (1) compressive yield strain: strain at the yield point; (2) compressive yield strength: stress at the yield point; and (3) crushing

[0256] These results indicate that the materials of the present invention are suitable for various applications. For example, Samples (1)-(2) are suitable for very short term applications, delivery method for HTR to keep it in place temporarily; Sample (3) is suitable for short term applications and delivery method for HTR to keep it in place temporarily; Sample (4) is suitable for short term applications. The high swelling may lead to good integration and good cellular infiltration; Sample (5) is suitable for longer term applications where stability is needed for healing and integration because its mass loss is significantly slower than that of formulations with more MSA; Sample (6) is suitable for longer term applications where stability is needed for healing and integration because its swelling is significantly more than in any other formulation, which maybe useful for enhanced tissue integration; Sample (7) is suitable for a longer term formulation to promote bone growth while maintaining stability because it lacks swelling and degrades at a slower rate as compared to formulations with higher HTR contents; Sample (8) is suitable for longer term needs where the sucrose is added to allow for cellular infiltration, the presence of the sucrose may help improve tissue integration; and Sample (9) is suitable for systems where stability is vital to success.

Example 13

[0257] Multi-Stage Curing

[0258] A curable admixture is made according to Formulation F below.

[0259] Formulation F

Ingredient	Weight
dimethacrylated anhydride of sebacic acid	300 mg
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	300 mg
dimethacrylated polyethylene glycol	400 mg
α-tricalcium phosphate	10 mg
$CaCO_3$	10 mg
$CaCl_2$	10 mg
DL-camphoquinone	5 mg
N-phenylglycine	5 mg
Bioplant ® HTR ®	1000 mg

[0260] The curable admixture made according to Formulation F is separated into equal portions: A and B. 5 mg of benzoyl peroxide (oxidizing component of a redox initiator system) is mixed into portion A. The resulting portion A is placed into one barrel of a multi-barrel syringe. 5 mg of N;N-dimethyl-p-toluidine (DMPT) (reducing component of a redox initiator system) is mixed into portion B. The resulting portion B is placed in to another barrel of the multi-barrel syringe.

[0261] Contents of the two barrels of the syringe are thoroughly mixed to partially cure the resulting mixture. The partially cured mixture is then applied to the tissue site and further cured by exposure to radiation. Barrel configurations can be either single with two-coaxial barrels or double, where one or both barrel(s) is covered to reduce light penetration.

Example 14

[0262] This example illustrates the invention with the first embodiment of the crosslinkable prepolymer.

[0263] Curable admixtures are formed by mixing two crosslinkable prepolymers: (1) dimethacrylated anhydride of sebacic acid and (2) dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane) with a bone substitute: (Bioplant® HTR®) as follows.

[0264] Formulation A

Ingredient	Weight
dimethacrylated anhydride of sebacic acid	325 mg
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	175 mg
DL-camphorquinone	5 mg
N-phenylglycine	5 mg
Bioplant ® HTR ®	510 mg

[0265] The dimethacrylated anhydride of sebacic acid is formed by reacting sebacic acid with methacrylic anhydride by heating at reflux and the dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane is formed by reacting 1,3-bis(p-carboxyphenoxy) propane with methacrylic anhydride by heating at reflux. DL-camphorquinone is used as a photoinitiator. This material is designed to be significantly resorbed in about 6-9 weeks when cured.

[0266] Formulation B

Ingredient	Weight
dimethacrylated anhydride of sebacic acid	175 mg
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	325 mg
DL-camphorquinone	5 mg
N-phenylglycine	5 mg
Bioplant ® HTR ®	510 mg

[0267] This material is designed to be significantly resorbed in about 9 months.

Example 15

[0268] This example illustrates the invention with the second embodiment of the crosslinkable prepolymer.

[0269] Formulaction C

Ingredient	Weight
dimethacrylated anhydride of sebacic acid	125 mg
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	125 mg
Poly(1,3-bis(p-carboxyphenoxy) propane:sebacic acid) (80:20)	250 mg
Irgacure 651 (Ciba-Geigy)	1 mg
Bioplant ® HTR ®	501 mg

[0270] Poly(1,3-bis(p-carboxyphenoxy) propane: sebacic acid) (80:20) ("Poly(CPP:SA) (80:20)") is a 80:20 (molar ratio) linear co-polymer of 1,3-bis(p-carboxyphenoxy) propane and sebacic acid. It is synthesized according to the procedure described in the Rosen et al. *Biomaterials,* 4, 131, (1983); Domb and Langer, *J. Polym. Sci.,* 23, 3375, (1987).

Example 16

[0271] This example illustrates the invention with the third embodiment of the crosslinkable prepolymer. The formulations are examples of a curable admixture formed by mixing (1) a crosslinkable prepolymer having at least two polymerizable terminal groups and a hydrophilic region with (2) bone substitute.

[0272] Formulation D

Ingredient	Weight
polyester bis-methacrylate	254.6 mg
demineralized bone powder	256.2 mg
DL-camphorquinone	4.42 mg
N-phenylglycine	2.54 mg
Bioplant ® HTR ®	517.76 mg

[0273] The polyester bis-methacrylate is prepared according to the method described in Example 1 of WO01/74411.

[0274] Formulation E

Ingredient	Weight
poly(D,L-lactide$_{50}$-co-ε-caprolactone)-hexanediol$_{20/1}$-methacrylate	250 mg
α-tricalcumphosphate	250 mg
DL-camphorquinone	1.2 mg
N-phenylglycine	1.1 mg
Bioplant ® HTR ®	502.3 mg

[0275] The poly(D,L-lactide$_{50}$-co-ε-caprolactone)-hexanediol$_{20/1}$-methacrylate is prepared according to the method described in WO 01/74411.

Example 17

[0276] The following experiment was conducted to study the bone ingrowth after extraction of molars and immediate fixation of an implant and placement of the curable admixture of the present invention. Formulation D of Example 3 was used.

[0277] Seven female sheep, ages 3 to 5 years, and thus having mature dentition, were used in the experiment. Two weeks prior to the extraction of teeth, the general health and dentition of the sheep were examined. If necessary, medication was used for de-vermification. Two days prior to the extraction, lateral and oblique pre-operation X-rays of the teeth to be removed were taken. One day prior to extraction, feeding was stopped and prophylactic AB (Excenel® RTU) and NSAID (Finadyne®) were administered. The next day (day 0) the P3 and P4 molars were extracted from both the left and right mandibles of the sheep. Preoperative medication of AB (Excenel® RTU) and Methylprednisolon (0.5 mg/kg, IM) was administered. The curable admixture in Example 3, was applied and cured in layers. The maximum thickness of each layer is about 5 mm. The light source was a standard dental 3M light in the visible light range. For each layer, the light was applied for 80 seconds.

[0278] In the left mandible, two titanium implants (Ankylos®), one normal and one modified with a square neck, were placed in one extraction socket. No implant was placed in the other socket. Bioplant® HTR® was mixed with Platelets Rich Plasma (PRP) and placed in the first socket around the implants as well as in the socket without implants. Bioplant® HTR® was then combined with the light curable polymer and placed in the first socket around the neck of the implants and in the occlusal part of the second socket without the implants. The strength of the mixture was from about 30 to about 40 N/m^2.

[0279] In the right mandible, two titanium implants (Ankylos®), one normal and one modified with a square neck, were placed in one extraction socket. No implant was placed in the other socket. Bioplant® HTR® was mixed with marrow bleeding and placed around the implants and in the socket without implants. Bioplant® HTR® was then combined with the light curable polymer and placed around the neck of the implants and in the occlusal part of the socket without the implants.

[0280] On days 1-3 AB (Excenel® RTU) (1 mg/kg) was administered. On day 30, 90 and 180 conventional and intra-oral X-rays were taken. On day 180, the sheep were euthanized and biopsies were performed for histological test.

Example 18

[0281] The lower anterior incisor of Patient A was falling out due to advanced gingival and bone disease. Pre-operative X-ray revealed that there was almost no bone around the tooth (98% gone, bone resorbed because of gem infection). Abscess and infection were observed. The tooth was about 99% mobile and had to be held in place with fingers. If a normal apicoectomy were conducted, the tooth would not have survived (i.e., it would have fallen out).

[0282] After debridement of the area around the tooth, the curable admixture, Formulation D, was applied around the lower portion of the tooth in layers. Each layer was about 5 mm thick. After the application of each layer, the material in that layer was hardened in situ with blue dental light (source: 3M® Light) for about 80 seconds. The next layer was applied immediately after the previous layer was hardened. After the desirable stability and thickness was reached and esthetic shape or gingiva was obtained, the surgical flap was repositioned and sutured closed. The tooth was immediately stable, functional, and free of significant micro-movement following the surgery.

Example 19

[0283] The upper left central incisor of Patient B had a bone void of 98% due to the tooth extraction and the failed grafting of the socket area with Algipore® (General Medical, UK) graft material. Infection and graft failure resulted not only the loss of a portion of the Algipore® graft, but also the destruction of the entire buccal plate and the adjacent bone. The failed Algipore® was surrounded by infected soft tissue.

[0284] The failed Algipore® was first surgically removed. After debridement of the area, a large bone void was revealed. A metal implant was planted into the bone void with hand instrumentation and stabilized by bone at the apex of the defect. There was only about 2 mm stabilization bone at the apex. Next, the curable admixture made according to Example 3, Formulation D, was applied around the implant in layers of approximately 5 mm or less and cured (hardened) with standard dental light for about 80 seconds. After the first layer was hardened, the next layer was added and cured. More layers were added and cured until the desired thickness for stability and esthetics was reached. The complete graft with cured material of the present invention was shown to support the metal implant. Next, the soft tissue around the implant was sutured. An immediate post-operative temporary jacket was added and placed in function (e.g., contact for chewing). The implant was immediately functional, stable, and free of significant micro-movement. Bone growth was observed around the metal implant. There was no infection.

Example 20

[0285] In addition to the synthesis method described in Example 1, methacrylated sebacic acids (MSA) and (1,3-bis(carboxyphenoxy))propyl dimethacrylate (CPPDM) were prepared according to the procedure described by Tarcha et al. *J. Polym. Sci, Part A, Polym. Chem.* (2001), 39, 4189. The MSA was synthesized by reacting sebacyl chloride and

methacrylic acid at 0° C. in the presence of triethylamine and dichloromethane. The CPPDM was prepared by reacting methacrylocyl and 1,3-bis(p-caboxyphenoxy) propane (CPP) at 0° C. in the presence of triethylamine and dichloromethane.

Example 21

[0286] Nine samples were prepared as follows:

[0287] 50 wt %: 50 wt % LC:Bioplant® HTR® (where LC is 100 wto/o MSA);

[0288] 45 wt %: 45 wt %:10 wt % LC: Bioplant® HTR®:sucrose (where LC is 100 wt % MSA);

[0289] 50 wt %: 50 wt % LC:Bioplant® HTR® (where LC is 50 wt % MSA and 50 wt % CPPDM);

[0290] 75 wt %: 25 wt % LC: Bioplant® HTR® (where LC is 100 wt % MSA);

[0291] 75 wt %: 25 wt % LC: Bioplant® HTR® (where LC is 90 wt % CPPDM and 10 wt % MSA);

[0292] 90 wt %: 10 wt % LC: sucrose (where LC is 90 wt % CPPDM and 10 wt % MSA);

[0293] 90 wt %: 10 wt % LC: Bioplant® HTR® (where LC is 90 wt % CPPDM and 10 wt % MSA);

[0294] 90 wt %: 5 wt %:5 wt % LC:Bioplant® HTR® sucrose (where LC is 90 wt % CPPDM, and 10 wt % MSA); and

[0295] 100 wt % LC (where LC 90 wt % CPPDM and 10 wt % MSA).

Example 22

[0296] Photopolymermization

[0297] To photopolymerize the samples in Example 8, an initiating system with ethyl 4-dimethylaminobenzoate in conjunction with an equal amount of camphorquinone was used. The ethyl 4-dimethylaminobenzoate and camphorquinone were dissolved in ethanol and added to each of the nine samples of Example 8 at 0.5 wt % relative to the total solids content (LC/HTR/sucrose combined).

[0298] The mixture was packed into Teflon molds containing 5 mm holes, placed between two glass slides and exposed to a 450 nm visible light source to produce 1 mm thick disks for in vitro degradation experiments (Example 10 below) or 10 mm thick cylinders for in vitro mechanical strength testing (Example 11 below). Such in vitro tests provide good initial assessment as to whether the material would be useful for orthopedic or dental applications. For example, (1) high compressive yield strength indicates that the material is suitable for immediate dental implant purposes, because such dental implants would be able to withstand the biting and/or chewing forces immediately; and (2) percentage of mass loss within a certain time period indicates how fast the material would resorb in vivo and provide a situs for bone/tissue growth.

Example 23

[0299] Degradation Experiments

[0300] In the disks prepared in Example 9 (5 mm in diameter×1 mm in thickness) were placed in individual tubes. The tubes were filled with approximately 1.5 ml of phosphate buffered saline (adjusted to pH 7.4) and the tubes were placed in a shaker incubator set to 37° C.; the buffer was removed and replaced every 1-2 days. Samples were removed periodically, weighed wet, then dried and reweighed. This allowed for calculation of the equilibrium swelling values as well as the mass loss over time. Data was collected in triplicate.

Example 24

[0301] Mechanical Strength Tests

[0302] The cylinders prepared in Example 9 (5 mm in diameter×10 mm in height) were used for the mechanical strength tests. Unconstrained uniaxial compression test were used to evaluate the mechanical properties of the cylinders at room temperature. Standard method was used to calibrate a 500 N load cell before testing. Five specimens of the each sample were mounted on a mechanical analyzer with the calibrated load cell. Specimens that broke at obvious flaws (e.g., water pocket or air pocket formation) were discarded. Strain was calculated from crosshead displacement. Stress was calculated from the load and cross-sectional area.

[0303] The ends of the samples were checked to make sure they are parallel to each other. Samples containing sucrose (i.e., Samples 2, 6, and 8) were soaked in de-ionized water overnight right before the testing date. All specimens were tested at 24° C. and ambient humidity.

[0304] The diameter of each sample was measured by a caliper to the nearest 0.01 mm at several points along its length. The minimum cross-sectional areas were calculated. The length of each specimen was measured to the nearest 0.01 mm. A concentric semi-circular mold was made to precisely mount the specimen at the center of the bottom anvil. Each specimen was mounted against the semi-circular mold between the surfaces of the anvils of the compression tool. The crosshead of the testing machine was adjusted until it just contacts the top of the compression tool plunger. The speed of the test was set at 1.3±0.3 mm/min. Loads and the corresponding compressive strain at appropriate intervals of strain were recorded to get the complete load-deformation curve. The maximum load carried by each specimen during the test (at the moment of rupture) was also recorded. If a specimen was relatively ductile, the speed was increased to 6 mm/min after the yield point had been reached; and the machine was run at this speed until the specimen breaks. The end point of the test was when the specimen was crushed to failure.

[0305] The following properties were calculated: (1) compressive yield strain: strain at the yield point; (2) compressive yield strength: stress at the yield point; and (3) crushing load: the maximum compressive force applied to the specimen, under the conditions of testing, that produces a designated degree of failure.

Example 25

[0306] Results and Discussion

[0307] The results of the degradation experiment (Example 10) and mechanical strength tests are summarized below.

TABLE 1

Results of testing for LC/BioPlant ® HTR ® formulations.

Sample[1]	LC[2] (wt %)	HTR (wt %)	Sucrose (wt %)	Compressive yield strain (%)	Compressive yield strength (MPa)	Crushing Load (MPa)	Integrity lost (days)	Swelling wt % in water	% Mass loss (# days)
1	50[3]	50	0	—	12.59 (±2.441)	—	4	slight amount, 50 wt %	43 ± 2 (20)
2	45[3]	45	10	—	4.365 (±1.334)[6]	—	4	slight amount, 50 wt %	49 ± 3 (18)
3	50[4]	50	0	—	—	—	6	slight amount, 50 wt %	35 ± 2 (21)
4	75[3]	25	0	—	—	—	8	100 wt %	62 ± 4 (21)
5	75[5]	25	0	6.285 (±1.30)	18.81 (±3.107)	19.06 (±3.15)	11	50 wt %	45 ± 2 (44)
6	90[5]	0	10	5.186 (±0.4822)	9.295 (±1.249)[6]	22.44 (±4.908)	11	>200 wt %	56 ± 6 (44)
7	90[5]	10	0	6.484 (±0.3490)	23.19 (±1.612)	—	36	slight amount, 50 wt %	40 ± 4 (48)
8	90[5]	5	5	9.082 (±1.229)	21.79 (±2.834)[6]	22.92 (±2.584)	36	slight amount, 50 wt %	47 ± 2 (48)
9	100[5]	0	0	5.878 (±0.8676)	11.67 (±3.028)	14.36 (±4.121)	56	75 wt % after 36 days	40 ± 3 (36)

[1]Photopolymerization conditions: 0.5 wt % camphorquinone, 0.5 wt % ethyl 4-dimethylaminobenzoate, λ = 450 nm
[2]MSA = methacrylated sebacic acid, CPPDM = (1,3-bis(carboxyphenoxy))propyl dimethacrylate
[3]composition = 100 wt % MSA
[4]composition = 50 wt % MSA/50 wt % CPPDM
[5]composition = 10 wt % MSA/90 wt % CPPDM
[6]soaked in deionized water to remove sucrose prior to testing

[0308] These results indicate that the materials of the present invention are suitable for various applications. For example, Samples (1)-(2) are suitable for very short term applications, delivery method for Bioplant® HTR® to keep it in place temporarily; Sample (3) is suitable for short term applications and delivery method for Bioplant® HTR® to keep it in place temporarily; Sample (4) is suitable for short term applications. The high swelling may lead to good integration and good cellular infiltration; Sample (5) is suitable for longer term applications where stability is needed for healing and integration because its mass loss is significantly slower than that of formulations with more MSA; Sample (6) is suitable for longer term applications where stability is needed for healing and integration because its swelling is significantly more than in any other formulation, which maybe useful for enhanced tissue integration; Sample (7) is suitable for a longer term formulation to promote bone growth while maintaining stability because it lacks swelling and degrades at a slower rate as compared to formulations with higher Bioplant® HTR® contents; Sample (8) is suitable for longer term needs where the sucrose is added to allow for cellular infiltration, the presence of the sucrose may help improve tissue integration; and Sample (9) is suitable for systems where stability is vital to success.

Example 26

[0309] Multi-Stage Curing

[0310] In A curable admixture is made according to Formulation below.

Ingredient	Weight
dimethacrylated anhydride of sebacic acid	300 mg
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	300 mg
dimethacrylated polyethylene glycol	400 mg
α-tricalcium phosphate	10 mg
$CaCO_3$	10 mg
$CaCl_2$	10 mg
DL-camphorquinone	5 mg
N-phenylglycine	5 mg
Bioplant ® HTR ®	1000 mg

[0311] The curable admixture made according to Formulation is separated into equal portions: A and B. 5 mg of benzoyl peroxide (oxidizing component of a redox initiator system) is mixed into portion A. The resulting portion A is placed into one barrel of a multi-barrel syringe. 5 mg of N,N-dimethyl-p-toluidine (DMPT) (reducing component of a redox initiator system) is mixed into portion B. The resulting portion B is placed in to another barrel of the multi-barrel syringe.

[0312] Contents of the two barrels of the syringe are thoroughly mixed to partially cure the resulting mixture. The partially cured mixture is then applied to the tissue site and further cured by exposure to radiation. Barrel configurations can be either single with two-coaxial barrels or double, where one or both barrel(s) is covered to reduce light penetration.

para toluidine in 2 mL poly(ethylene glycol) diacrylate. Mn 258 (PEGDA~300). This component was stored in the refrigerator and was used for about a week before discarding.

[0320] For the following examples, the particular formulations used are:

Example	Formulation			
29	90% MCPP	10% PEG DMA		
30	90% MCPP	10% PEG DMA		formulated with 25% filler
31	75% MCPP	25% PEG DMA		
32	75% MCPP	25% PEG DMA		formulated with 25% filler.
33	90% MCPP	10% PEG DMA	5% SA	
34	50% MCPP	25% PEGDMA600	25% MSA	
35	40% MCPP	15% PEG DMA	15% MSA	30% $CaCO_3$
36	50% MCPP	25% PEGDMA600	25% MSA	formulated with 25% Bioplant ® HTR ®
37	50% MCPP	25% PEGDMA600	25% MSA	formulated with 50% Bioplant ® HTR ®
38	65% MCPP	15% PEGDMA600	10% MSA	10% $CaCO_3$
39	65% MCPP	15% PEGDMA600	20% MSA	
40	65% MCPP	15% PEGDMA600	20% MSA	formulated with 30% Bioplant ® HTR ®
41	90% MCPP	10% PEGDMA600 - chemical cure		
42	75% MCPP	25% PEGDMA600 - chemical cure		
43	75% MCPP	25% PEGDMA600 - chemical cure		formulated with 25% Bioplant ® HTR ®
44	70% MCPP	25% PEGDMA600	5% MSA	
45	70% MCPP	25% PEGDMA600	5% MSA - chemical cure	
46	55% MCPP	20% PEGDMA600	15% MSA	10% $CaCO_3$
47	55% MCPP	20% PEGDMA600	15% MSA - chemical cure	10% $CaCO_3$

Example 27

[0313] Chemical and Light Initiator Components

[0314] Component A was prepared by mixing 0.5 g benzoyl peroxide and 0.5 g camphorquinone in 2 ml N-methyl-2-pyrrolidone (NMP). This mixture was stored in an opaque container in the refrigerator and was used for about a week before discarding.

[0315] A second version of component A was prepared by mixing 0.5 g benzoyl peroxide and 0.5 g camphorquinone in 10% v/v ethyl acetate. Then 2 ml poly(ethylene glycol) diacrylate, Mn ~300 was added, and vortexed to mix. This mixture was stored in an opaque container in the refrigerator and was used for about a week before a fresh solution was made.

[0316] Component B was prepared by mixing 0.25 g 4-ethyl-dimethyl amino benzoate and 0.15 mL dimethyl para toluidine in 2 mL poly(ethylene glycol) diacrylate. Mn 258 (PEGDA~300). This component was stored in the refrigerator and was used for about a week before discarding.

Example 28

[0317] Chemical Initiator Components

[0318] A solution of component A having only chemical curing properties was prepared by mixing 0.5 g benzoyl peroxide in 2 ml NMP. This mixture was stored in the refrigerator and was used for about a week before discarding.

[0319] A solution of component B having only chemical curing properties was prepared by mixing 1.0 mL dimethyl

Example 29

[0321] MCPP was combined with the PEG DMA and mixed thoroughly (for 2-5 minutes). Component A from Example 27 was added and mixed until the color and consistency was evenly dispersed. Then component B from Example 27 was added and mixed thoroughly. Because of the high viscosity of the sample, care must be taking during mixing of both component A and component B to obtain a homogeneous mixture. The mixture was allowed to stand for approximately 30 seconds with occasional mixing before transfer to a mold 12 mm in diameter where it was packed down to remove air pockets. Dental blue light was directed onto the sample for 1 minute (or up to 2 minutes for other preferred applications), during which the sample was rotated to promote uniformity. After cooling, the sample was removed from the mold.

[0322] 90% MCPP, 10% PEG DMA

Ingredient	Weight
Methacrylated poly(1,3-bis(p-carboxy-phenoxy) propane	4.5 g
dimethacrylated polyethylene glycol 600	500 μl
Component A	100 μl
Component B	100 μl

[0323] For testing of this sample, the sample was removed from the mold and cut down to a 25.4 mm height and placed in phosphate buffered saline (PBS) at 37° C. for 24 hours. Compressive strength testing demonstrates a max load of 870±326 N and a max stress of 8±3 mPa.

Example 30

[0324] The sample can be prepared as described in Example 29, using the Component A and Component B as prepared in Example 27. The Bioplant® HTR® will be stirred into the sample with Component A.

[0325] 90% MCPP, 10% PEG DMA—formulated with 25% filler

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	3.375 g
dimethacrylated polyethylene glycol 600	375 μl
Bioplant ® HTR ®	1.25 g
Component A	100 μl
Component B	100 μl

[0326] The Bioplant® HTR® in this formulation adds strength and increase resorption time.

Example 31

[0327] The sample of was prepared as described in Example 29, using the Component A and Component B as prepared in Example 27.

[0328] 75% MCPP, 25% PEG DMA

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	3.75 mg
dimethacrylated polyethylene glycol 600	1.25 ml
Component A	100 μl
Component B	100 μl

[0329] After 24 hours preconditioning in PBS at 37° C., compressive strength was 7 MPa at 748 N max load for 1 sample and 10 MPa at 1174 N max load for another.

Example 32

[0330] The sample of was prepared as described in Example 29, using the Component A and Component B as prepared in Example 27. The Bioplant® HTR® was stirred into the sample with Component A.

[0331] 75% MCPP, 25% PEG DMA—formulated with 25% filler

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	2.813 g
dimethacrylated polyethylene glycol 600	0.932 ml
Bioplant ® HTR ®	1.25 g
Component A	100 μl
Component B	100 μl

[0332] After 24 hours preconditioning in PBS at 37° C., compressive strength was 11 MPa at 1201 N max load in one sample and 14 MPa at 1645 N max load in another.

Example 33

[0333] MCPP was combined with the PEG DMA and mixed thoroughly (for 2-5 minutes). Then the SA was mixed with the MCPP/PEG mixture. Component A from Example 27 was added and mixed until the color and consistency was evenly dispersed. Then component B from Example 27 was added and mixed thoroughly. The mixture was allowed to stand for approximately 30 seconds with occasional mixing before transfer to a mold 12 mm in diameter where it was packed down to remove air pockets. Dental blue light was directed onto the sample for 1 minute, during which the sample was rotated to promote uniformity. After cooling, the sample was removed from the mold.

[0334] 90% MCPP, 10% PEG DMA—with 5% SA

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	85.5 mg
dimethacrylated polyethylene glycol 600	95 mg
dimethacrylated anhydride of sebacic acid	50 mg
Component A	20 μl
Component B	20 μl

[0335] This formulation is made having increased plasticity and easier production than the admixture without SA.

Example 34

[0336] The sample can be prepared as described in Example 33, using the Component A and Component B as prepared in Example 27 and where MSA is used.

[0337] 50% MCPP, 25% MSA, 25% PEGDMA600

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	500 mg
dimethacrylated polyethylene glycol	250 mg
dimethacrylated anhydride of sebacic acid	250 mg
Component A	20 μl
Component B	20 μl

[0338] This sample is designed for fast resorption properties.

Example 35

[0339] The sample can be prepared as described in Example 33, using the Component A and Component B as prepared in Example 27. The $CaCO_3$ is stirred in with component A, MCPP, and PEG-DM.

[0340] 40% MCPP, 15% PEG DMA, 15% MSA, 30% $CaCO_3$ filler

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	2 g

-continued

Ingredient	Weight
dimethacrylated polyethylene glycol	0.75 g
dimethacrylated anhydride of sebacic acid	0.75 g
$CaCO_3$	1.5 g
Component A	100 μl
Component B	100 μl

[0341] This sample is designed for fast resorption properties, lower viscosity, moderate strength Example 36

[0342] The sample can be prepared as described in Example 33, using the Component A and Component B as prepared in Example 27.

[0343] 50% MCPP, 25% MSA, 25% PEGDMA600—formulated with 25% Bioplant® HTR® filler

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	1.875 g
dimethacrylated polyethylene glycol	0.938 g
dimethacrylated anhydride of sebacic acid	0.938 g
Bioplant ® HTR ®	1.25 g
Component A	100 μl
Component B	100 μl

[0344] This sample provides the strength and slow rate of degradation due to the HTR filler component as well as the high strength from the addition of the MSA.

Example 37

[0345] The sample can be prepared as described in Example 33, using the Component A and Component B as prepared in Example 27.

[0346] 50% MCPP, 25% MSA, 25% PEGDMA600—formulated with 50% Bioplant® HTR® filler.

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	1.25 g
dimethacrylated polyethylene glycol	0.625 g
dimethacrylated anhydride of sebacic acid	0.625 g
Bioplant ® HTR ®	2.5 g
Component A	100 μl
Component B	100 μl

[0347] This sample provides the strength and slow rate of degradation due to the HTR filler component as well as the high strength from the addition of the MSA. A similar formulation can be made with 25% or 30% Bioplant® HTR®.

Example 38

[0348] The sample can be prepared as described in Example 33, using the Component A and Component B as prepared in Example 27.

[0349] 65% MCPP, 10% MSA, 15% PEGDMA600, 10% $CaCO_3$

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	3.25 g
dimethacrylated polyethylene glycol	0.75 g
dimethacrylated anhydride of sebacic acid	0.50 g
$CaCO_3$	0.50 g
Component A	100 μl
Component B	100 μl

[0350] This sample is designed for strength and biodegradation times shorter than can be obtained with the addition of Bioplant® HTR®.

Example 39

[0351] The sample can be prepared as described in Example 33, using the Component A and Component B as prepared in Example 27.

[0352] 65% MCPP, 15% MSA, 20% PEGDMA600

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	3.25 g
dimethacrylated polyethylene glycol	0.75 g
dimethacrylated anhydride of sebacic acid	1.0 g
Component A	100 μl
Component B	100 μl

[0353] This sample is formulated for high strength.

Example 40

[0354] The sample can be prepared as described in Example 33, using the Component A and Component B as prepared in Example 27 with the addition of Bioplant® HTR®.

[0355] 65% MCPP, 15% MSA, 20% PEGDMA600—formulated with 30% Bioplant® HTR®

Ingredient	Weight
dimethacrylated anhydride of 1,3-bis(p-carboxyphenoxy) propane	3.25 g
dimethacrylated polyethylene glycol	0.75 g
dimethacrylated anhydride of sebacic acid	1.0 g
Bioplant ® HTR ®	1.5 g
Component A	100 μl
Component B	100 μl

[0356] This sample is formulated for high strength and good bone growth characteristics.

Example 41

[0357] MCPP was combined with the PEG and mixed thoroughly (for 2-5 minutes) until the texture was uniform. The mixture was then transferred to a mold 12 mm in

diameter where it was loosely packed. Component A from Example 28 was added and mixed thoroughly (2-3 minutes). Then component B from Example 28 was added and mixed thoroughly (2-3 minutes). The material was packed down in the mold to compress and remove air pockets (15-30 sec.) The sample was left in the mold for 2-3 hours for curing.

[0358] 90% MCPP, 10% MPEG—chemical cure

Ingredient	Weight
Methacrylated poly(1,3-bis(p-carboxyphenoxy) propane	4.5 g
PEG DMA 600	500 μl
Component A	100 μl
Component B	100 μl

[0359] For testing of this sample, the sample was removed from the mold and cut down to 25.4 mm height and placed in phosphate buffered saline (PBS) at 37° C. for 24 hours. Compressive strength for two samples using this formulation were: (a) 4 mPa at 489 N, and (b) 15 MPa at 1675 N.

Example 42

[0360] The sample of was prepared as described in Example 28, using the Component A and Component B as prepared in Example 28.

[0361] 75% MCPP, 25% MPEG—chemical cure

Ingredient	Weight
Methacrylated poly(1,3-bis(p-carboxyphenoxy) propane	3.75 g
PEG DMA 600	1.25 ml
Component A	100 μl
Component B	100 μl

[0362] After 24 hours preconditioning in PBS at 37° C., compressive strength was 12 MPa at 1324 N.

Example 43

[0363] The sample was prepared as described in Example 28, using the Component A and Component B as prepared in Example 28.

[0364] 75% MCPP, 25% MPEG, formulated with 25% Bioplant® HTR® filler—chemical cure

Ingredient	Weight
Methacrylated poly(1,3-bis(p-carboxyphenoxy) propane	2.81 g
PEG DMA 600	938 μl
Bioplant ® HTR ®	1.25 g
Component A	100 μl
Component B	100 μl

[0365] After 24 hours preconditioning in PBS at 37° C., compressive strength was 8 MPa at 938 N.

Example 44

[0366] MCPP was combined with the PEG DMA and mixed thoroughly. Then the MSA was mixed with the MCPP/PEG mixture for approximately 10 minutes. Component A from Example 27 was added and mixed for about 4 minutes. Then component B from Example 27 was added and mixed thoroughly (about 1 minute). The mixture was poured into a mold having a 6.3 mm inner diameter and a length of 12.6 mm. Dental blue light was directed onto the sample for 1 minute, with the sample rotated after 30 seconds. The sample was allows to cure for 2-3 hours and the mold was removed. The sample was then filed down to the desired length for compression testing. The samples were left in phosphate buffered saline solution at 37° C. for 24 hours before testing for strength.

[0367] 70% MCPP, 25% PEGDMA600, 5% MSA

Ingredient	Weight
Methacrylated poly(1,3-bis(p-carboxyphenoxy) propane	0.7 g
PEG DMA 600	250 μl
MSA	50 μl
Component A	20 μl
Component B	20 μl

Example 45

[0368] The sample was prepared as described in Example 31, except that light was not used on this sample. Component A and Component B were used as prepared in Example 28.

[0369] 70% MCPP 25% PEGDMA6005% MSA—chemical cure

Ingredient	Weight
Methacrylated poly(1,3-bis(p-carboxyphenoxy) propane	0.7 g
PEG DMA 600	250 μl
Bioplant ® HTR ®	50 μl
Component A	20 μl
Component B	20 μl

Example 46

[0370] The sample was prepared as described in Example 31, using the Component A and Component B as prepared in Example 27. The $CaCO_3$ was added after the MSA was mixed with the MCPP and PEG DMA and mixed for 10 minutes.

[0371] 55% MCPP 20% PEGDMA60015% MSA 10% $CaCO_3$

Ingredient	Weight
Methacrylated poly(1,3-bis(p-carboxyphenoxy) propane	0.55 g

-continued

Ingredient	Weight
PEG DMA 600	200 μl
$CaCO_3$	100 μg
Component A	20 μl
Component B	20 μl

Example 47

[0372] The sample was prepared as described in Example 33 except that no light was used. Component A and Component B were used as prepared in Example 28.

[0373] 55% MCPP 20% PEGDMA60015% MSA—chemical cure 10% $CaCO_3$

Ingredient	Weight
Methacrylated poly(1,3-bis(p-carboxyphenoxy) propane	0.55 g
PEG DMA 600	200 μl
$CaCO_3$	100 μg
Component A	20 μl
Component B	20 μl

Example 48

[0374] Four different formulations were prepared as described above with the addition of camphorquinone and ethyl 4-dimethylaminobenzoate. The samples were placed in tibia and zygoma defects in rabbits. These formulations provide different lengths of time for resorption, i.e., short acting and longer acting. The 4 formulations tested in rabbits are:

F1	90% MCPP	10% MSA	
F2	90% MCPP	10% MSA	formulated with 10% Bioplant ® HTR ® and $CaCO_3$
F3	90% MCPP	10% MSA	formulated with 25% Bioplant ® HTR ® and $CaCO_3$
F4	100% MSA		formulated with 25% Bioplant ® HTR ®

[0375] 10% sucrose and 10% gellaten were added as porogens.

[0376] The polymer samples were placed into defects in the rabbit tibia and zygoma (6 mm trephine on each), hardened with light, and evaluated at 4 or 8 weeks. Histological results show polymer resorption and bone growth at 4 and 8 weeks. Voids present in locations where the polymer materials were initially placed indicate the resorption of the polymer with subsequent regrowth of bone into the void. Generally, the anhydride polymer material resorbed and new bone formed and bridged normally. The materials used in this study did not appear to cause significant inflammation, rejection, necrosis, or foreign body reaction. Controls included empty (non-grafted) control defects. There were no adverse events with the anhydride alone, a anhydride and Bioplant® HTR®, or control sites in any location in any animal.

[0377] Generally, new bone was seen to bridge most of the defect in either the tibia **(FIGS. 1A and 1B)** or zygoma **(FIGS. 2A and 2B)** samples by 8 weeks in both the control **(FIGS. 1A and 2A)** and light hardened polymer containing the bone substitute Bioplant® HTR® **(FIGS. 1B and 2B)**. Fingers of new bone growth are seen near the periphery of the bony defect for both. The presence of the anhydride polymer and Bioplant® HTR® maintained and helped reconstitute the dimensions of the defects and provided scaffolding for the bone growth, as new growth was observed at the periphery where the anhydride was observed and resorbing as well around the Bioplant® HTR® materials in the depth of the defect.

What is claimed:

1. A initiator system for anhydride polymerization comprising:

(i) an initiator comprising:

a light radical generating component,

a chemical radical generating component, and

a solvent,

(ii) an amine accelerator comprising:

a light accelerator component,

a chemical accelerator component, and

a solvent,

wherein the polymer initiator system is used to initiate polymerization of a crosslinkable anhydride prepolymer.

2. The initiator system of claim 1, wherein the anhydride polymer system comprises a filler.

3. The initiator system of claim 1, wherein the light radical generating component is camphorquinone.

4. The initiator system of claim 1, wherein the chemical radical generating component is a peroxide or azo compound.

5. The initiator system of claim 3, wherein the chemical radical generating component is benzoyl peroxide (BPO), the light accelerator component is 4-ethyl-dimethylaminobenzoate, and the chemical accelerator component is dimethyl para toluidine.

6. The initiator system of claim 1, wherein the initiator solvent is a PEG polymer and the light radical generating component and chemical radical generating components are approximately 1:1 by weight.

7. The initiator system of claim 1, wherein the amine accelerator solvent is a PEG polymer and the light accelerator component and chemical accelerator component are approximately 5:3 by weight.

8. The initiator system of claim 1, wherein the light accelerator component and chemical accelerator component comprise a single compound.

9. The initiator system of claim 1, wherein the crosslinkable anhydride prepolymer comprises methacrylated carboxyphenoxypropane or methacrylated carboxyphenoxyhexane.

10. The initiator system of claim 9, wherein the crosslinkable anhydride prepolymer further comprises methacrylated sebacic acid.

11. A curable polymer composition comprising:

(i) an initiator comprising:

a chemical radical generating component, and

an optional light radical generating component;

(ii) an amine accelerator comprising:

a chemical accelerator component, and

an optional light accelerator component, and

(iii) a curable crosslinkable prepolymer comprising:

(a) an anhydride of a monomer or oligomer of a diacid or multifunctional acid and a carboxylic acid molecule which includes a crosslinkable group, wherein the crosslinkable group is an unsaturated hydrocarbon moiety; or

(b) a linear polymer selected from the group consisting of linear, hydrophobic biodegradable polymers and linear non-degradable hydrophilic polymers; and at least one monomer or macromer containing at least one free radical polymerizable group, wherein at least one of the monomers or macromers includes an anhydride linkage and a polymerizable group selected from the group consisting of acrylate or methacrylate; and

(iv) an optional filler.

12. The composition of claim 11 wherein the curable crosslinkable prepolymer comprises methacrylated carboxyphenoxypropane or methacrylated carboxyphenoxyhexane.

13. The composition of claim 12 wherein the curable crosslinkable prepolymer comprises methacrylated sebacic acid.

14. The composition of claim 11, further comprising a filler.

15. The composition of claim 14, wherein the filler is a ceramic, polymer, or polymer-ceramic hybrid bone substitute.

16. The composition of claim 15, wherein the bone substitute is Bioplant® HTR®, tricalcium phosphate, hydroxyapatite, or a hybrid thereof.

17. The composition of claim 15, wherein the filler is 10-50% by weight of the polymer composition.

18. The composition of claim 14, further comprising a growth factor material or an antibiotic.

19. A method of forming a polymer comprising:

(i) mixing

an initiator comprising a chemical radical generating component, and an optional light radical generating component;

an amine accelerator comprising a chemical accelerator component, and an optional light accelerator component; and

a curable crosslinkable prepolymer comprising:

(a) an anhydride of a monomer or oligomer of a diacid or multifunctional acid and a carboxylic acid molecule which includes a crosslinkable group, wherein the crosslinkable group is an unsaturated hydrocarbon moiety; or

(b) a linear polymer selected from the group consisting of linear, hydrophobic biodegradable polymers and linear non-degradable hydrophilic polymers; and at least one monomer or macromer containing at least one free radical polymerizable group, wherein at least one of the monomers or macromers includes an anhydride linkage and a polymerizable group selected from the group consisting of acrylate or methacrylate; and

to form an initiated polymer,

(iii) placing the initiated polymer into a final location, and

(iv) optionally shining light on the initiated polymer.

20. The method of claim 19, further comprising mixing a filler with the curable crosslinkable prepolymer.

21. The method of claim 19, wherein the filler is a ceramic, polymer, or polymer-ceramic hybrid bone substitute.

22. The method of claim 19, wherein the bone substitute is Bioplant® HTR®, tricalcium phosphate, hydroxyapatite, or a hybrid thereof.

23. The method of claim 20, wherein the final location is a tooth socket, bone cavity, or other bony void.

24. The method of claim 20, wherein the final location is in soft tissue.

25. The method of claim 20, wherein the polymer is formed during a spinal fusion.

26. The method of claim 19, wherein the prepolymer comprises methacrylated carboxyphenoxypropane, methacrylated carboxyphenoxyhexane, methacrylated sebacic acid.

27. A delivery system comprising the curable polymer system of claim 11 and at least one container.

28. The delivery system of claim 27, wherein the curable crosslinkable prepolymer is a putty.

29. The delivery system of claim 27, wherein the curable crosslinkable prepolymer is injectable.

30. The delivery system of claim 29, wherein the container is a syringe.

* * * * *

EXHIBIT L

CURRICULUM VITAE

ARTHUR ASHMAN, BS, D.D.S., FAGD, FICOI, FADI
177 Post Road West, Westport, CT 06880

EDUCATION

1957 BS	Queens College, NY. After completing 2 1/2 years of college via Professional Option
1961 D.D.S.	Columbia University, New York, NY School of Dental and Oral Surgery
1978 FAGD	Fellow, Academy of General Dentistry
1985 FAAID	Honored Fellow, American Academy of Implant Dentistry
1986 FICOI	Diplomate, International College of Oral Implantologists
1990 FADI	Fellow, Academy of Dentistry International
1993 ABOI	Diplomate, American Board of Oral Implantology-Implant Dentist

MILITARY SERVICE

1962-1964	Captain, U.S. Dental Corps ULM, West Germany

LICENSURE

1961	New York State Boards
1961	National Boards

SPECIALTY

1962-1966	Oral Surgery
1975-1993	Rehabilitative Dentistry with Implants

FIELDS OF MAJOR EXPERIENCE

Implant Dentistry
Rehabilitative Dentistry
Research – Bioplant® HTR™ Synthetic Bone Alloplast
Inventor – Bioplant® HTR™ Synthetic Bone Alloplast
Founder, Ashman Department of Implant Dentistry, New York University, College of Dentistry

PRIVATE DENTAL PRACTICE

1964 - 1991 in New York, NY

PROFESSIONAL APPOINTMENTS

1991-present	Clinical Professor of Dentistry - Arthur Ashman Dept. of Implant Dentistry, New York University College of Dentistry, New York, NY
1987-1990	Associate Clinical Professor of Dentistry - Dept. of Biomaterials, New York University College of Dentistry, New York, NY
1967-1978	Head of Dental Research, Mt. Sinai Research Center (ATRN), New York, NY
1971-1975	Research Associate Professor, Columbia University College of Physicians and Surgeons, New York, NY
1968-1974	Cleft Palate, Maxillofacial Prosthetic Team, Mt. Sinai Hospital, New York, NY
1964-1968	Clinical Assistant, Prosthetic, Crown and Bridge Depts., Mt. Sinai Hospital, New York, NY
1964-1966	Clinical Assistant Professor, Diagnosis Dept., Columbia University School of Dental & Oral Surgery, New York, NY

HONORARY AND PROFESSIONAL SOCIETIES

1993-present	Diplomate, American Board of Oral Implantology
1991-present	Member, Academy of Osseointegration
1986-present	Diplomate, International College of Oral Implantology
1985-present	Honored Fellow, American Academy of AAID
1984-1985	National V.P. Academy of Implant Dentistry
1983-1984	President, NE District Academy of Implant Dentistry
1982-1983	V.P. NE District Academy of Implant Dentistry
1980-present	1842 Club, Columbia University School of Dental & Oral Surgery
1979-present	Y.M.P.L. (Young Man's Philanthropic League)
1977-present	Fellow, Academy of General Dentistry
1971-1977	Chairman, Dental Division, United Jewish Appeal
1970-present	Member, American Medical Writers Association
1969-1980	Member, New York State Society for Medical Research
1968-present	Member, Academy of Implant Dentistry
1968-present	Member, Institute for Advanced Dental Research
1964-present	Member, American Association for the Advancement of Science
1964-1968	Member, Academy of Endosseous Implants
1964-present	Member, Academy of General Dentistry
1964-present	Member, Academy of Psychosomatic Medicine
1964-present	Member, Academy for the Study of Headache
1961-present	Member, American Dental Association
1961-present	New York State Dental Society
1961-present	Member, New York City First District Dental Society
1961-present	Member, Eastern Dental Society
1961-present	Member, Midtown Dental Society
1961-present	Member, Alpha Omega Dental Fraternity

LECTURES AND SEMINARS

1972-present Over 500 lectures given at dental schools, societies, conventions, and organizations

Seminars averaging 6 to 8 per year

Examples of Lectures - (1972 - Present)

Columbia University School of Dental and Oral Surgery, New York, NY
New York University College of Dentistry, New York, NY
Israeli Dental Society, Haifa, Israel
American Academy of Implant Dentistry
Greater New York Dental Meeting, New York, NY
Academy of Implant Dentistry, Atlantic City, NJ
Eleventh District Dental Society, Long Island, NY
Tenth District Dental Society, Jamaica, NY
Mt. Sinai Hospital, New York, NY
American Dental Association, New York, NY
Perio-Prosthetic Study Group, New York, NY
Academy of Implant Dentistry, Las Vegas, NV
Eastern Dental Society, New York, NY
First District Dental Society, New York, NY
San Francisco Dental Society, San Francisco, CA
Midtown Dental Society, New York, NY

Examples of Seminars and Courses - (1967 - Present)

U.S.A. (Yearly 1969 to present)
Argentina (1997)
Belgium (1993, 1997, 1999, 2000)
Chile (1997)
Denmark (1997)
England (1972, 1975, 1978, 1981, 1985, 1991, 1992, 1993, 1995, 1999)
France (1972, 1974, 1982, 1983, 1989, 1992, 1993, 1996, 1999, 2000)
Germany (1981, 1984, 1992, 1993, 2000)
Israel (1967, 1970, 1972, 1974, 1978, 1979)
Italy (1972, 1975, 1980, 1981, 1983, 1984, 1993, 1996)
Hong Kong (1997, 1998, 1999)
Hungary (1995, 1996)
Japan (1978, 1995)
Korea (1997, 1998, 1999)
Malaysia (1995, 1996, 1997)
Mexico (1973, 1978, 1985, 1987, 1989, 1991)
Philippines (1995, 1996, 1997)
Singapore (1995, 1996, 1997, 1998)
Spain (1991, 1992, 1993)
Switzerland (1984, 1995)
Taiwan (1995, 1996, 1998)

Thailand (1995, 1996, 1997)

RESEARCH EXPERIENCE AND PROJECTS

1969-present	Researcher: Research projects with dental implants and Bioplant® HTR® Synthetic Bone replacement systems at various Universities with other investigators.
1971-1974	Columbia University School of Dental & Oral Surgery: Porous Polymers and Bone Growth - with Dr. M. Moss
	Columbia University School of Dental & Oral Surgery: Porous Polymers and Bone Growth - with Dr. P. Kamen
1987-present	New York University: Bioplant® HTR® in conjunction with Drs. A. Schulman, L. Salman, S. Stahl
	New York University: Growth factors grafted on Bioplant® HTR® with implants - with Dr. Craig, Dr. Tarnow
	New York University: Dog studies -Bioplant® HTR® and cylinder implants - with Dr. Tarnow, Dr. Cranin
	New York University: Bioplant® HTR® in extraction sockets and immediate post-extraction implant - with Dr. Tarnow, Dr. Froum, Dr. LeGeros, Dr. Glickman
1971-1977	Mt. Sinai Hospital - Dog studies - Bioplant® HTR® tooth implants - with Dr. J. Klatell, Chief of Dentistry
1972-1976	Batelle Columbus: with Drs. Duga and Donavant
1972-1976	Weissman Institute: Tel Aviv, Israel with Dr. Binderman
1973-1975	Brown University, Harvard University, Tufts University: Acrylic resin tooth implant - animal and clinical studies with Dr. Milton Hodosh
1974	University of Buffalo: with Dr. Jack Armitage
1975-1978	University of Tennessee: with Dr. Kinstle
1980-1981	University of Bologna: with Dr. Muratori
1983-1984	Weissman Institute: Tel Aviv, Israel with Dr. Binderman
1983-1984	University of Bologna: with Dr. Muratori

1984 University of Munich: with Dr. D. Schlager

Recipient of six issued patents on HTR polymer from U.S. Patent Office. Many foreign patents as well.

PUBLICATIONS

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